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Review – Bladder Cancer – Editor's Choice

Checkpoint Inhibitors in Urothelial Carcinoma—Future Directions and Biomarker Selection

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Abstract

Context: Several recent phase 2 and 3 trials have evaluated the efficacy and toxicity of checkpoint inhibitor (CPI) therapy for urothelial carcinoma (UC) in the metastatic, localized muscle-invasive UC (MIUC), upper tract UC, and non–muscle-invasive bladder cancer (NMIBC) disease state.
Objective: To assess the outcomes and toxicity of CPIs across the treatment landscape of UC and contextualize their application to current real-world treatment.
Evidence acquisition: We queried PubMed, Web of Science, and EMBASE databases and conference abstracts to identify prospective trials examining CPIs in UC. The primary endpoints included overall survival, recurrence-free survival, and toxicity (when available). A secondary analysis included biomarker evaluation of response.
Evidence synthesis: We identified 21 trials, 12 phase 2 and nine phase 3 trials, in which a CPI was used for metastatic UC (seven), MIUC (nine), and NMIBC (five). For first-line (1L) metastatic UC, concurrent chemotherapy with CPIs failed to show superiority. Improved overall and progression-free survival for switch maintenance avelumab (after achieving stable disease or response with induction systemic chemotherapy) has established the current standard of care for 1L metastatic UC. A single-agent CPI is a consideration for patients unable to tolerate chemotherapy. CPIs in the perioperative setting are limited to only the adjuvant treatment with nivolumab after radical surgery for MIUC in patients at a higher risk of recurrence based on pathologic stage. Only pembrolizumab is approved by the Food and Drug Administration for carcinoma in situ unresponsive to bacillus Calmette-Guérin (BCG) in patients who are not fit for or who refuse radical cystectomy. Trials investigating CPIs in combination with multiple immune regulators, antibody drug conjugates, targeted therapies, antiangiogenic agents, chemotherapy, and

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radiotherapy are enrolling patients and may shape the future treatment of patients with UC.

Conclusions: CPIs have an established role across multiple states of UC, with broadened applications likely to occur in the future. Several combinations are being evaluated, while the development of predictive biomarkers and their validation may help identify patients who are most likely to respond.

Patient summary: Our findings highlight the broad activity of checkpoint inhibitors in urothelial carcinoma, noting the need for further investigation for the best application of combinations and patient selection to patient care.

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1. Introduction

Treatment options for patients with metastatic urothelial carcinoma (mUC) have increased with potential therapies, including chemotherapy and/or immunotherapy, targeted therapy, and now antibody-drug conjugates. Unfortunately, the durable clinical benefit remains suboptimal, with few patients living >24 mo. While cisplatin-based chemotherapy improves survival for patients with mUC, recurrence remains common. The identification of immune checkpoint inhibitors (CPIs), antibody-drug conjugates, and fibroblast growth factor receptor (FGFR) inhibition ushered in a renaissance of systemic therapies that reshaped the therapeutic landscape for mUC. Currently, three CPIs are approved by the Food and Drug Administration (FDA) and used, while others have also been evaluated for urothelial carcinoma (UC). In Europe, CPI use is limited to cisplatin-ineligible patients who are PD-L1 positive for first line (1L) and after cystectomy. While the accumulated success of CPIs has improved survival for a proportion of patients, the nuances of timing, combination, sequencing, and biomarker-based patient selection remain an active area of investigation and an area of unmet need. In this review, we summarize the current use of CPIs across stages of UC, including mUC, nonmetastatic muscle-invasive UC (MIUC), and non–muscle-invasive bladder cancer (NMIBC), to highlight the efficacy and safety of CPI treatment in UC.

2. Evidence acquisition

2.1. Search strategy

We searched PubMed, EMBASE, and Web of Science with the terms "urothelial carcinoma" and "immunotherapy" from 2016 to 2022. We elected to limit the search from 2016 to ensure the inclusion of only the most recent trials, identifying 5420 articles. From this search, 1804 citations were screened. The lead and senior author manually reviewed each article (Supplementary Fig. 1).

2.2. Inclusion criteria

The collaborative review was limited to primary research and biomarker analysis of phase 2–3 clinical trials in UC that involved at least 30 patients and described outcomes of only patients with UC.

2.3. Data review

Individual reports were reviewed and summarized. A total of four papers were included in the final review.

3. Evidence synthesis

The efficacy and toxicity of each trial were reviewed and summarized, with manuscripts grouped by 1LmUC, localized MIUC, and NMIBC disease states. In addition, a biomarker analysis of these trials was included as supporting information.

3.1. Metastatic urothelial carcinoma

UC was one of the first tumors demonstrating a response to immune CPIs [1,2]. The history of phase 1 and early phase 2 trials in mUC have previously been described [3–6]. We focused on large trials of CPIs, reporting at least their primary endpoint of recurrence, comparing CPIs with standard of care in the 1L metastatic setting. Before the inception of these landmark trials, patients were treated with chemotherapy or immunotherapy in a 1L setting, often depending on their performance status, tumor PD-L1 immunohistochemistry (IHC) staining status, medical comorbidities, fitness for cisplatin, goals of care, patient preference, and provider experience since guidelines recommended the use of either chemotherapy or CPIs in the 1L setting in cisplatin-ineligible patients. Three large phase 3 trials shaped the landscape of 1L mUC. Each trial had three treatment arms and included over 1000 patients with progression-free survival (PFS) and overall survival (OS) as primary endpoints. Two trials evaluated the concurrent combination of CPIs and systemic chemotherapy (IMvigor130 and KN361), while the third evaluated the combination of anti-CTLA and anti–PD-1 (DANUBE). These trials also evaluated the safety and efficacy of CPI monotherapy versus chemotherapy and contributed important information about single-agent CPI activity.

IMvigor130 was a placebo-controlled phase 3 trial that enrolled 1213 patients randomized 1:1:1 to three treatment arms [7]. The treatment arms included atezolizumab plus gemcitabine and platinum chemotherapy (arm A), atezolizumab monotherapy (arm B), and gemcitabine and platinum chemotherapy plus placebo (arm C). Investigators prespecified cisplatin eligibility before randomization, and 53–58% of patients were considered cisplatin ineligible, although 70% of arm A and 66% of arm C received carbo-

platin. PD-L1 was deemed high (IC2/3) in 23–24% in each arm. The median PFS was significantly greater in arm A (8.2 mo, 95% confidence interval [CI] 6.5–8.3 mo) than in arm C (6.3 mo, 6.2–7.0; stratified hazard ratio [HR] 0.82, 95% CI 0.70–0.96, one-sided $p = 0.007$). At the first data cut-off at a median follow-up for survival of 11.8 mo (interquartile range [IQR] 6.1–17.2 mo), there was a trend toward longer OS in arm A, 16.0 mo (95% CI 13.9–18.9 mo), compared with 13.4 mo (12.0–15.2 mo) in arm C (stratified HR 0.83, 95% CI 0.69–1.00; one-sided $p = 0.027$), but this was not significant based on the prespecified analysis, while the updated analysis in 2022 did not show a significant difference in OS. The median OS was 15.7 mo (95% CI 13.1–17.8 mo) for arm B and 13.1 mo (11.7–15.1 mo) for arm C (stratified HR 1.02, 95% CI 0.83–1.24). In an exploratory analysis, the primary group that benefited in arm B was the PD-L1–high population (IC2/3), with median OS that was not reached compared with 17.8 mo (10.0 mo–not estimable [NE]) in arm C (stratified HR 0.68, 95% CI 0.43–1.08), while OS for PD-L1–low population (IC0/1) was 13.5 mo (95% CI 11.1–16.4 mo) in arm B versus 12.9 mo (11.3–15.0 mo) in arm C (unstratified HR 1.07, 95% CI 0.86–1.3). Owing to the hierarchical study design, OS comparisons of arm B versus arm C could not be tested formally since arm A versus arm C had not met statistical significance for OS. The overall response rates (ORRs) were 47% in arm A (95% CI 43–52%), 23% in arm B (95% CI 19–28%), and 44% in arm C (95% CI 39–49%), with a median duration of response of 8.5 mo (7.2–10.4 mo), NE (15.9-NE), and 7.6 mo (6.3–8.5 mo), respectively. Thus, single-agent atezolizumab had almost a 50% lower response rate, but of those who did respond (higher ORR in PD-L1+ tumors), a number of patients achieved a durable response. Safety favored arm B, with only 60% experiencing any grade (Gr) of treatment-related toxicity (15% Gr 3–4, 1% Gr 5), compared with 96% in arms A and B, with 81% experiencing any Gr 3–5 toxicity. An early press release of the final OS of Imvigor130 reported that an OS benefit was not reached, and a publication is anticipated in 2023 [8].

KEYNOTE-361 (KN361) was an open-label phase 3 trial that compared the outcomes of 1010 patients randomized to pembrolizumab plus platinum-based chemotherapy, pembrolizumab single agent, or platinum-based chemotherapy [9]. Rates of carboplatin use were 55–56% in the chemotherapy plus pembrolizumab and chemotherapy alone groups. The median follow-up was 31.7 mo (IQR 27.7–36.0 mo), and the median PFS was 8.3 mo (95% CI 7.5–8.5 mo) in the pembrolizumab plus chemotherapy group versus 7.1 mo (95% CI 6.4–7.9 mo) in the chemotherapy group (HR 0.78, 95% CI 0.65–0.93; $p = 0.003$), which did not meet the prespecified boundary of 0.0019 (one-sided alpha = 0.005). The addition of pembrolizumab to chemotherapy did not improve OS (median 17.0 mo, 95% CI 14.5–19.5 mo) compared with chemotherapy alone (median 14.3 mo, 95% CI 12.3–16.7 mo; HR 0.86 [95% CI 0.72–1.02], $p = 0.0407$). The median OS was 15.6 mo (95% CI 12.1–17.9 mo) with pembrolizumab monotherapy versus 14.3 (12.3–16.7) mo with chemotherapy alone (HR 0.92, 95% CI 0.77–1.11). As an exploratory analysis of PD-L1+ patients (combined positive score [CPS] $\geq$10), the median OS was 16.1 mo (95% CI 13.6–19.9 mo) with pembrolizumab monotherapy compared with 15.2 (11.6–23.3) mo with chemotherapy alone (HR 1.01, 95% CI 0.77–1.32). ORRs were, respectively, 54.7% (49.3–60.0%), 30.3% (25.2–35.8%), and 44.9% (39.6–50.2%) for pembrolizumab plus chemotherapy, pembrolizumab monotherapy, and chemotherapy alone. Again, the median duration of response was longer in the pembrolizumab monotherapy group (28.2 mo, 13.5–NE) than in the combination therapy (8.5, 8.2–11.4) or chemotherapy alone (6.2, 5.8–6.5) group, although fewer patients achieved responses with pembrolizumab alone. Serious adverse events (Gr $\geq$3) were observed less frequently in patients treated with pembrolizumab monotherapy (12%) than in those treated with pembrolizumab plus chemotherapy (29%) or chemotherapy (26%).

DANUBE was an open-label phase 3 trial comparing durvalumab monotherapy, durvalumab, and tremelimumab, and chemotherapy [10], 1032 patients were randomized, and the median follow-up was 41.2 mo (37.9–43.2 mo). Cisplatin-eligible patients were 56–57% in each group. The primary analysis of DANUBE was OS in patients with PD-L1–high tumors based on Ventana SP263 assay treated with durvalumab alone compared with chemotherapy. The median OS was 14.4 mo (95% CI 10.4–17.3 mo) in the durvalumab group and 12.1 (10.4–15.0) mo in the chemotherapy group (HR 0.89, 95% CI 0.71–1.11, two-sided $p = 0.30$). The median OS was 15.1 (13.1–18.0) mo in the durvalumab plus tremelimumab group and 12.1 (10.9–14.0) mo in the chemotherapy group (HR 0.85, 95% CI 0.72–1.02, two-sided $p = 0.075$). The median PFS was 2.3 mo (95% CI 1.9–3.5 mo) in the single-agent durvalumab group, 3.7 (3.4–3.8) mo in the durvalumab plus tremelimumab group, and 6.7 (5.7–7.3) mo in the chemotherapy group. The objective response rates (investigator-assessed complete or partial response) were 26% in the durvalumab group, 36% in the durvalumab plus tremelimumab group, and 49% in the chemotherapy group. The median duration of a response was 9.3 (5.8–20.5) mo for patients treated with durvalumab monotherapy, 5.7 (5.6–6.2) mo for chemotherapy, and 11.1 (7.9–18.5) mo for patients treated with durvalumab and tremelimumab. A secondary endpoint of OS in the durvalumab plus tremelimumab versus chemotherapy in the high PD-L1 population showed a significant benefit with a doublet CPI regimen (0.74, 95% CI 0.59–0.93). Serious treatment-related adverse events (as defined in the protocol) occurred in 9% in the durvalumab group, 23% in the durvalumab plus tremelimumab group, and 16% in the chemotherapy group.

While all three trials showed responses to CPI monotherapy, there is a critical question for patients in the 1L setting: "Is single-agent CPI an option without prior chemotherapy?" In 2023, only pembrolizumab was an option for 1L patients who are ineligible for any platinum-based chemotherapy, while atezolizumab indications were withdrawn for UC [11]. Multiple biomarker studies have evaluated tumor and tumor microenvironment (TME)-related factors associated with response or resistance to CPIs. An integrated analysis of Imvigor210, a single-arm phase 2 trial of atezolizumab in patients with mUC (cisplatin-ineligible

1L and 2L settings), found that the structure of the TME had the most important effect on response to atezolizumab [2]. Similar to the findings from melanoma [12], tumors infiltrated with CD8+ T cells had the highest response to CPIs (inflamed). Still, those without T cells (desert) and those with stromal infiltration, and excluded immune cells (excluded) had limited response to atezolizumab. The addition of an anti–TGF-β antibody to a CPI improved response to the CPI in an ectopic cancer model as validation that targeting the stromal TME may enhance response to CPIs. A complimentary analysis was performed of a pan-cancer cohort of patients with metastatic cancer treated with pembrolizumab [13]. A T-cell inflamed gene expression profile (GEP) was an independent predictor of response, regardless of tumor mutational burden (TMB). Across tumor types, patients with both high TMB and enhanced GEP had a greater response rate than only one signature (37–57% vs 11–42%), while patients with low TMB and low GEP had a low response rate (0–9%). In a follow-up biomarker analysis of KN-052 (1L cisplatin ineligible) and KN-045 (second-line after platinum), multiple biomarkers (PD-L1, TMB, $Tceff_{inf}$-GEP, and a stromal signature) were compared between two cohorts treated with pembrolizumab [14]. While a high TMB (defined as >175 mutations/genome) was associated with a higher response rate in both trials, with areas under the receiver operating characteristic curves of 0.67 (95% CI 0.59–0.75) for KN-052 and 0.65 (95% CI 0.54–0.75) for KN-045, and so was $Tceff_{inf}$GEP (0.63 [95% CI 0.54–0.73] for KN-052 and 0.62 [95% CI, 0.54–0.75] for KN-045). In contrast, PD-L1 and a TGF-β/stromal signature were associated with a response only in the KN-052 trial but not in the KN-045 trial. These data may be confounded by potential variability based on the line of therapy and heterogeneity of new-generation sequencing assays and other unmeasured biomarkers across the two trials and disease states, yet suggest that response to pembrolizumab seems to correlate with TMB.

In summary, the three phase 3 trials evaluating CPIs in 1L mUC did not change practice but provided critically important information about the activity of CPIs in UC. First, chemotherapy, regardless of cisplatin or carboplatin, appeared to have a greater ORR than CPIs. Second, while the ORR of CPIs was less than that of chemotherapy, the "tail on the curve" or durability appeared to be superior to that of chemotherapy. Finally, concurrent combination therapy with both chemotherapy and CPIs was not a successful strategy. It is unclear why the outcomes of chemotherapy and CPIs did not appear additive or synergistic. Several hypotheses have been suggested. First, the patient populations that benefit from chemotherapy and CPIs may overlap. Second, the use of corticosteroids as an antiemetic may have reduced the efficacy of CPIs. Third, the chemotherapy agents may have been somewhat immunosuppressive (eg, lymphodepletion) or have induced nonimmunogenic cell death; there might be a lack of appropriate biomarker selection, or statistical designs employed. Patients whose tumors expressed a high level of PD-L1 did better with atezolizumab in the arm B of Imvigor130; PD-L1 assessment did not consistently identify patients likely to respond to CPIs across trials where different PD-L1 assays, antibody clones, methods, compartments, and cut points were used. Many of the challenges related to selecting patients based on the PD-L1 biomarker are the wide prevalence of biomarker-"positive" tumors in some trials and the variability of positive testing between trials and disease states. For example, DAKO 22C3 showed a 30% CPS $\geq$10 prevalence in the KN052 trial but 45–50% in the KN361 trial. The SP263 for DANUBE routinely identifies 55% of patients as PD-L1 positive, while SP142 for Imvigor trials was positive in about 23%. Discordant expression of PD-L1+ biomarkers, potential issues with analytical validity, and variable biologic significance may all render risk stratification and biomarker validation very challenging. Synthesizing the results of these trials, the concept of sequential therapy rather than the concurrent combination of CPIs and chemotherapy may leverage the accelerated disease control of chemotherapy and the long-term benefit of CPIs. The use of PD-L1 IHC remains a critical feature in Europe where treatment of 1L and postcystectomy patients are restricted for PD-L1–positive tumors only [15].

3.1.1. *Switch maintenance strategy*

Despite the lack of a clear benefit of concurrent CPIs with chemotherapy, sequential use of chemotherapy followed by a CPI has both pragmatic and scientific justification. First, more patients treated with CPIs progress quickly, while chemotherapy can induce a cytocidal reduction in tumor volume in more patients. Cell death caused by chemotherapy could increase antigens and improve immune recognition. Thus, switching to CPI maintenance after chemotherapy could bolster immune response, and try to prevent recurrence and progression with lower toxicity compared with chemotherapy [16]. The first randomized trial of switch maintenance was the phase 2 GU14-182 trial [17]. After stable disease or response to four to eight cycles of platinum-based chemotherapy, 55 patients were randomized to pembrolizumab 200 mg intravenously (IV) every 3 wk for up to 24 mo or matched placebo with a planned crossover for progression (which occurred in about half of patients). Patients on pembrolizumab received an average of eight cycles (IQR 4–15 cycles). The median PFS was significantly longer with switch maintenance pembrolizumab (5.4 mo [95% CI 3.1–7.3 mo]) than with placebo (3.0 mo [95% CI 2.7–5.5 mo], HR 0.65, log-rank p = 0.04). Potentially due to the small sample size, a significant OS advantage of switch maintenance was not identified; the median OS was 22 mo (95% CI 12.9 mo to not reached) with pembrolizumab and 18.7 mo (95% CI 11.4 mo to not reached) with placebo (HR 0.91, 95% CI 0.52–1.59).

The JAVELIN Bladder 100 trial was a phase 3 trial of switch maintenance therapy [18]; 700 patients with 1L mUC with disease stabilization or response after four to six cycles of gemcitabine and cisplatin (GC) or carboplatin were randomized 1:1 to either avelumab plus best supportive care (BSC) or BSC alone. The median OS was significantly greater in patients treated with avelumab, at a median of 21.4 mo (95% CI 18.9–26.1 mo) compared with 14.3 mo with BSC (95% CI 12.9–17.9 mo; stratified HR for death 0.69; 95% CI 0.56–0.86; repeated CI 0.54–0.92; p = 0.001). A second primary endpoint of the trial was survival in

patients with PD-L1+ tumors (56% of the cohort), which showed a greater degree of benefit with avelumab with median OS not reached (20.3–NE) compared with BSC alone (17.1 [13.5–23.7]; HR 0.56, 0.4–0.79, $p < 0.001$) in that group. Adverse events led to discontinuation in 11.9% of patients; 29% had immune-related adverse events and two patients died from CPI toxicity. A comprehensive biomarker analysis of the JAVELIN Bladder 100 trial was performed, which identified multiple features potentially associated with a higher degree of benefit with avelumab [19]. Multiple putative biomarkers, including interferon (IFN)-γ and IFN-α response gene expression, APOBEC mutation signature, and CD8+ T-cell expression, were evaluated. Interestingly, the authors identified that higher-affinity FcγR binding alleles that may mediate avelumab activity through antibody-dependent cell-mediated cytotoxicity were associated with a greater benefit. In contrast, mutations in FGFR3 and neutrophil expression modules were associated with less benefit with avelumab. To attempt to manage the complexity of response to CPIs, the authors developed a 19-feature clinical/molecular/cellular model that could identify patients with more benefit with avelumab (HR [> vs ≤median] 2.45, 95% CI 1.155–5.196, $p = 0.0195$) with validation in the Imvigor130 cohort (HR [> vs ≤median] 2.02, 95% CI 1.191–3.438, $p = 0.0092$). No benefit was identified on BSC alone, suggesting that this signature may potentially be predictive for avelumab rather than prognostic of UC. The quality of life was not compromised with switch maintenance avelumab [20].

3.1.2. Future directions

Switch maintenance is the gold standard for patients able to receive cisplatin- or carboplatin-based chemotherapy. However, patients with limited renal function (eg, glomerular filtration rate <30 ml/min), Gr ≥2 neuropathy, or poor performance status (Eastern Cooperative Oncology Group score 3) may not be able to receive even carboplatin-based chemotherapy, and this is reflected in the US FDA approval for pembrolizumab for platinum-ineligible patients regardless of PD-L1 expression. In Europe, atezolizumab or pembrolizumab is recommended only for cisplatin-ineligible patients who are PD-L1 positive [15]. Future investigation of feasible, safe, and effective combination regimens for 1L platinum-ineligible patients has the greatest urgency. The identification of agents that provide additive or synergistic effects in combination with CPIs will be essential to advance the field further. Current trials in 1L are listed in Table 1.

The most likely candidate class for combination with CPIs is the antibody-drug conjugates. EV-103 dose escalation and cohort A enrolled 45 untreated cisplatin-ineligible patients with mUC [21,22]. Patients were treated with enfortumab vedotin (EV) 1.25 mg/kg IV on days 1 and 8 and pembrolizumab 200 mg/m^2 IV on day 1, every 21 d; safety was the primary endpoint, with secondary endpoints of objective response rate, duration of response, and OS. The objective response rate for the combination was 73.3%, with a complete response rate of 15.6%. The responses observed were durable, with a median response duration of 25.6 mo and median OS of 26.1 mo. Safety was manageable, with neuropathy, skin reactions, and fatigue as the most common adverse events. These very promising data were confirmed in the randomized cohort K of this trial with a 64.5% objective response rate and durable responses with the combination of pembrolizumab and EV, which may possibly lead to accelerated approval in cisplatin-ineligible patients with mUC [23].

3.2. Muscle-invasive bladder cancer

While currently not FDA approved for preoperative/neoadjuvant therapy for patients with MIUC, multiple phase 2 trials have identified reasonable pathologic response rates with neoadjuvant CPIs. Adjuvant therapy with a CPI showed a significant improvement in disease-free survival (DFS) in one large phase 3 trial but no benefit in another trial with another CPI.

3.2.1. Neoadjuvant CPIs

PURE-01 was an open-label single-arm phase 2 trial of neoadjuvant pembrolizumab prior to radical cystectomy (RC) in cisplatin-eligible muscle-invasive bladder cancer (MIBC) [24]. Two centers recruited 114 patients, many of whom had cT3 tumors prior to RC (50/114 [44%]). An inclusion criterion for PURE01 was that all patients had residual cancer after transurethral resection of bladder tumor (TURBT) prior to a neoadjuvant CPI. All patients received three cycles of pembrolizumab (200 mg IV every 3 wk) followed by RC within 3 wk of completion (median time to RC for the initial 50 patients was 22 d, and the IQR was 15–30 d). Patients not demonstrating a clinical response to neoadjuvant pembrolizumab underwent chemotherapy prior to surgery (7/114 patients, 6.1%). The primary endpoint was pathologic complete response (pCR; defined as ypT0N0) achieved in 42% (21/50), with pathologic downstaging to <pT2 in 54% (27/50). PD-L1 CPS ≥10% (70% of patients, or 35/50) correlated with pT0 status at the time of RC, with 54.3% (19/35 patients) with PD-L1 CPS ≥10% compared with only 13.3% (2/15) with PD-L1 CPS <10% ($p = 0.011$). An updated report identified pCR in 55/143 patients (38.5%, 95% CI 30.5–46.5%), downstaging 80 patients (55.9%, 95% CI 47.4–64.2%) [25]. The median event-free survival (EFS; defined by the protocol) was not reached in the intention-to-treat (ITT) cohort, and the 12- and 24-mo EFS was 84.5% (78.5–90.9%) and 71.7% (62.7–82%), respectively. Response to pembrolizumab was associated with a higher TMB and alterations in DNA damage repair genes. A subsequent evaluation of RNA-based subtypes in PURE01 identified enhanced response with basal subtype (63% response) and specifically with basal tumors with enhanced immune infiltration (100% response) [26].

ABACUS was an open-label, multicenter, single-arm phase 2 trial of neoadjuvant atezolizumab in 95 patients with cT2-T4aN0M0 UC who were ineligible for or who refused neoadjuvant chemotherapy (NAC) [27]. Similar to in PURE01, patients were required to have residual cancer after TURBT that could be measured for a response. Patients received two cycles of atezolizumab (200 mg IV every 3 wk), with RC performed at a median of 5.6 wk after receiving the last dose of atezolizumab. The primary endpoint of ABACUS was pCR, achieved in 31% (27/88), with an addi-

Table 1 – Clinical trials in progress involving checkpoint immunotherapy in first-line metastatic patients

Trial	Arms	Phase	Patients	Outcome	clinicaltrials.gov	Estimated completion	Estimated study completion
NILE	Gem/cis or gem/carbo + durva ± treme vs Gem/cis or gem/carbo	3	1292	OS, PFS, ORR	NCT03682068	June 30, 2023	October 30, 2023
MAIN-CAV	Gem/cis or gem/carbo followed by avelumab + cabozantinib maintenance Gem/cis or gem/carbo followed by avelumab maintenance	3	654	OS, PFS, ORR, AE	NCT05092958	December 10, 2024	December 10, 2024
JAVELIN Bladder Medley	Avelumab maintenance + SG or M6223 or NKTR-255 vs Avelumab maintenance	2	252	PFS, AE, OS, ORR, PK	NCT05327530	August 5, 2026	August 24, 2026
PRESERVE3	Gem/cis vs gem/carbo + trilaciclib followed by maintenance avelumab + trilaciclib Gem/cis or gem/carbo followed by maintenance avelumab	2	92	PFS, ORR, OS	NCT04887831	March 1, 2023	May 1, 2024
TROPHY U-01 (cohort 6)	SG (arm 1) vs SG + ZIM (arm 2) SG + ZIM + Dom (arm 3) Gem/cis or gem/carbo followed by maintenance avelumab	2	226	OS, DOR, PFS, AE	NCT03547973	July 1, 2024	July 1, 2026
CheckMate-901	Nivo/ipi Gem/cis/nivo Vs gem/cis or gem/carbo	3	1307	OS in cis ineligible, cis eligible, PD-L1+, PFS	NCT03036098	June 15, 2023	July 15, 2025
EV-302	EV + pembro Gem/cis or gem/carbo	3	990	OS, PFS by BICR, PFS by investigator, ORR, DOR,	NCT04223856	November 30, 2023	September 30, 2027

AE = adverse event; BICR = blinded independent central review; carbo = carboplatin; cis = cisplatin; DOR = duration of response; durva = durvalumab; EV = enfortumab vedotin; gem = gemcitabine; ipi = ipilimumab; nivo = nivolumab; ORR = overall response rate; OS = overall survival; pembro = pembrolizumab; PFS = progression-free survival; PK = pharmacokinetics; treme = tremelimumab.
Columns include trial name (where available), agents tested, trial phase, number of patients, described primary outcomes, clinicaltrials.gov number, estimated completion, and study completion dates from clinicaltrials.gov.

tional major pathologic response in seven more patients (38%). Two-year DFS and OS were 68% (95% CI 58–76%) and 77% (95% CI 68–85%), respectively, while the percentage of those achieving pCR was 85% (95% CI 65–94%, 24 mo) [28]. PD-L1 positivity by SP142 (40% of the cohort) was not associated with the pathologic response rate. PD-L1–positive tumors had a pCR rate of 37.1% (95% CI 21.5–55.1%), compared with 24.5% (95% CI 13.3–38.9%) for PD-L1–negative tumors ($p = 0.21$) [13]. A pathologic response in ABACUS correlated with pretreatment CD8+ infiltration, with a higher response rate (17/42, 40.5%) if the tumor harbored a CD8+ T-cell count of less than the median (8/41, 19.5%, $p = 0.04$) [13]. At RC, the median CD8+ increased by 78% after two doses of atezolizumab (before vs after CD8+ infiltrate, $p = 0.004$).

NABUCCO was a single-arm feasibility trial in 24 patients with stage III UC who were treated with two doses of ipilimumab (3 mg/kg on days 1 and 22) and two doses of nivolumab (anti–PD-1; 1 mg/kg on days 22 and 43) prior to RC [29]. Patients either were ineligible for (54%) or refused (46%) NAC. All patients tolerated CPIs, and no surgery was delayed longer than 12 wk from the end of CPI treatment. Dual checkpoint blockade resulted in Gr 3–4 immune-related adverse events in 55% of patients, but only one patient had a delay in time to RC by 4 wk. Eleven of 24 (46%) experienced pCR, and 14 (58%) had no remaining invasive cancer (pCR or ypTaN0 /TisN0). The response was associated with CD8+ T cells and a greater increase in tertiary lymphoid structures.

Using doublet CPIs, durvalumab, and tremelimumab, a phase 2 trial was reported, which enrolled 28 cisplatin-ineligible patients with high-risk MIUC [30]. Patients were treated with two cycles of durvalumab (1500 mg/kg) and tremelimumab (75 mg/kg) prior to RC. Gr $\geq$3 immune-related adverse events were observed in 21% of patients, and 86% of patients underwent cystectomy per protocol. Three patients had delayed cystectomy, of whom two had a delay due to immune-related adverse events (median delay 35 d). The pCR rate (including pTis) was 37.5%, and the downstaging rate to $\leq$pT1N0 was 58.3%. Tumors with higher numbers of tertiary lymphoid structures had better pathologic and clinical responses to CPIs.

3.2.2. *Neoadjuvant trials of CPIs with chemotherapy*

While CPI monotherapy had a favorable pathologic response in multiple phase 2 trials, PD-L1–negative patients who were cisplatin eligible may have missed out on potentially curative therapy. To potentially improve the response of CPIs, several phase 2 and 3 trials combining CPIs with NAC were initiated. While the phase 3 trials of neoadjuvant CPIs have not reported complete data on pathologic and clinical responses, several phase 2 trials have reported pathologic response rates. Pembrolizumab was combined with GC for four cycles in 39 patients [31] in the LCCC 1520 trial. Downstaging to ypT $\leq$1 occurred in 56%, including 45% of patients with cT3/cT4, and the pCR was 36% (14/39). All but one patient had RC with a median time to surgery of 46 d, and 69% received all four cycles; serious

adverse events occurred in 74%. At a median follow-up of 15.7 mo (11.5–21.9 mo), 21% (eight patients) had a relapse. The median EFS (protocol defined) was not identified, and PD-L1+ IHC was not associated with a greater rate of downstaging (67% vs 47%, $p = 0.25$). In a similar phase 2 trial of neoadjuvant GC (four planned cycles) plus atezolizumab in 44 patients [32], downstaging was reported in 69% (27/44) and pCR in 41% (16/44). There was no significant association with PD-L1 status (100% response in four IC 2/3 patients compared to 68% in the other 34). Treatment-related adverse events of Gr ≥3 occurred in 59%, with the most common being neutropenia in 36%. Among responders, no patient relapsed after a median follow-up of 23.6 mo (range: 12.0–38.2 mo). Additional phase 2 trials showed promising results with chemotherapy plus CPIs, while multiple randomized phase 3 trials comparing chemotherapy and CPIs with chemotherapy are awaiting results but have not been reported (Table 2). Trials in progress evaluating CPIs in MIBC for patients electing bladder preservation are described in Table 3.

3.2.3. *Adjuvant CPIs*

While individual adjuvant trials of platinum-based chemotherapy after RC have never definitively shown a significant OS benefit, meta-analyses have suggested a modest improvement in OS [33]. Historically, about 30% of patients who require adjuvant chemotherapy cannot receive it [34]. The improved tolerability of CPIs has led to significant enthusiasm for this modality in the postoperative setting. Indeed, perioperative immunotherapy has become standard in both lung cancer and melanoma [35,36]. The first phase 3 trial to report the outcomes of adjuvant CPIs was Imvigor010 [37], a randomized open-label trial of observation compared with atezolizumab in 809 patients with high-risk MIUC, defined as ypT2-T4a or ypN+ in NAC-treated patients (48%) or pT3-4a or pN+ in NAC-naïve patients. The median DFS was 19.4 mo (95% CI 15.9–24.8 mo) in the atezolizumab group compared with 16.6 mo (95% CI 11.2–24.8 mo) in the observation group (stratified HR 0.89 [95% CI 0.74–1.08], two-sided log-rank $p = 0.24$) with no significant difference in OS (stratified HR 0.85 [95% CI 0.66–1.09]). Gr 3–4 treatment-related adverse events occurred in 37 (10%) patients treated with atezolizumab, with no toxicity-related death noted.

CheckMate274 had a similar design and inclusion criteria to Imvigor010, but differed by comparing nivolumab with a placebo in the control arm [38]. In addition, while only 6–7% of IMvigor010 patients had upper tract UC (UTUC), 21% of CheckMate274 patients had UTUC. The rate of NAC prior to radical surgery (including nephroureterectomy) was 43%. The median DFS in the ITT population was 20.8 mo (95% CI 16.5–27.6 mo) in the nivolumab group and 10.8 mo (95% CI 8.3–13.9 mo) in the placebo group. The 6-mo rates of DFS in the ITT population were 74.9% with nivolumab and 60.3% with placebo (HR 0.70, 98.22% CI 0.55–0.90, $p < 0.001$). PD-L1+ tumors had an even greater benefit from adjuvant nivolumab (HR 0.55, 98.72% CI 0.35–0.85, $p < 0.001$). In a subgroup analysis, renal pelvis and ureteral tumors had a limited response to nivolumab (HR 1.23 [0.63–2.23] and HR 1.56 [0.7–3.48]), although the study was not powered to test the benefit in this subgroup. Gr ≥3 treatment-related adverse events occurred in 17.9% of the nivolumab group compared with 7.2% in the placebo group. There were two deaths from pneumonitis in the group treated with nivolumab. Nivolumab became FDA approved in the USA for adjuvant treatment of MIUC in August 2021 for patients at a high risk for recurrence based on pathologic stage. Nivolumab is approved in Europe as adjuvant therapy for patients at a high risk for recurrence whose tumors are PD-L1 positive. The OS analysis from CM274 is event driven, and the data are still immature. A considerable concern for the difference in the two trials was the significant early censoring that occurred in Imvigor010, which may have impacted DFS in the control group. A meta-analysis of the two trials found no significant difference in DFS in patients receiving adjuvant nivolumab or atezolizumab, but the control arms had a significantly different outcome in placebo-treated patients with significantly more recurrences and shorter DFS (log-rank test $p = 0.039$) [39]. The trial was discontinued in 40 patients from IMVigor010 compared with only seven in CM274. A simulation of censoring suggests that censoring of up to 14% (rather than the 20% that occurred) could have resulted in an HR of 0.83 (95% CI 0.69–0.99, $p = 0.049$) and a positive result of IMVigor010. Biomarker research from Imvigor010 identified a subset of patients most likely to benefit from adjuvant atezolizumab [40]. Of the 809 patients in the trial, 581 were evaluated for circulating tumor DNA (ctDNA) at cycle 1 day 1 (C1D1; before treatment) and cycle 3 day 1 (C3D1). At C1D1, 37% (214/581) had detectable ctDNA, and these patients were at a significantly greater risk for recurrence (DFS HR 6.3, 95% CI 4.45–8.92, $p < 0.0001$). While there was no difference in DFS for ctDNA-negative patients with atezolizumab compared with observation, ctDNA-

Table 2 – Clinical trials in progress involving checkpoint immunotherapy in muscle-invasive bladder cancer patients

Trial	Arms	Phase	Patients	Outcome	clinicaltrials.gov	Estimated completion	Estimated study completion
NIAGRA	Durvalumab + GC + RC/PLND vs GC + RC/PLND	3	988	pCR + EFS	NCT03732677	June 30, 2023	June 30, 2026
Keynote B15	EV + Pembro + RC/PLND	3	784	pCR + EFS	NCT04700124	December 23, 2026	December 23, 2026
GAP S2011	Avelumab + Gcarbo + RC/PLND vs RC/PLND	2	196	pCR	NCT04871529	April 30, 2027	April 30, 2029

EFS = event-free survival; EV = enfortumab vedotin; GC = gemcitabine and cisplatin; Gcarbo = gemcitabine and carboplatin; pCR = pathologic complete response; Pembro = pembrolizumab; PLND = pelvic lymph node dissection; RC = radical cystectomy.
Columns include trial name (where available), agents tested, trial phase, number of patients, described primary outcomes, clinicaltrials.gov number, estimated completion, and study completion dates from clinicaltrials.gov.

Table 3 – Clinical trials in progress involving checkpoint immunotherapy in chemoradiotherapy-treated patients

Trial	Arms	Phase	Patients	Outcome	clinicaltrials.gov	Estimated completion	Estimated study completion
SN1806	CRT ± atezo	3	475	BI-EFS	NCT03775265	June 1, 2027	June 1, 2027
Keynote-992	CRT ± pembro	3	636	BI-EFS	NCT04241185	June 10, 2029	June 10, 2031
Bladderspar	Atezo after CRT	3	77	DFS	NCT03697850	June 15, 2025	February 15, 2029
NCT03993249	CRT ± nivo	3	78	Locoregional control	NCT03993249	August 1, 2022	December 1, 2023
SunRISe-2	TAR-200 + cetrelimab vs CRT	3	550	BI-EFS	NCT04658862	December 30, 2026	December 31, 2028
NCT03768570	CRT ± durvalumab	2	190	DFS	NCT03768570	March 31, 2025	March 31, 2026

Atezo = atezolizumab; BI-EFS = bladder intact event-free survival; CRT = chemoradiotherapy; DFS = disease-free survival; nivo = nivolumab; pembro = pembrolizumab.
Columns include trial name (where available), agents tested, trial phase, number of patients, described primary outcomes, clinicaltrials.gov number, estimated completion, and study completion dates from clinicaltrials.gov.

positive patients had longer DFS with adjuvant atezolizumab (HR 0.58, 95% CI 0.43–0.79, p = 0.0024; median DFS: 5.9 compared with 4.4 mo). Treatment with atezolizumab led to clearance of ctDNA in 18.2% (18/99) of ctDNA-positive patients by C3D1 compared with only 3.8% in those in the control arm (3/79), resulting in longer DFS (HR 0.26 [95% CI 0.12–0.56], p = 0.0014; median DFS: 5.7 mo vs not reached) and OS. These findings have identified ctDNA as a putative prognostic and predictive biomarker in this disease state, and the results need validation. The Imvigor011 trial has been initiated to test atezolizumab versus placebo in ctDNA-positive patients with MIUC at a high risk of recurrence for such validation. In this trial design, only patients with detectable ctDNA after surgery will be randomized to atezolizumab or a placebo, making them a higher-risk group than those in IMvigor010.

3.3. *Non–muscle-invasive bladder cancer*

3.3.1. *BCG unresponsive*

Based on CPI activity in the advanced and adjuvant settings, as well as retrospective analyses implicating the PD-(L)1 pathway as a resistance mechanism to intravesical bacillus Calmette-Guérin (BCG) therapy [41,42], the role of CPIs in NMIBC has been investigated in multiple single-arm phase 2 trials. In KEYNOTE-057, patients with BCG-unresponsive carcinoma in situ (CIS) with or without papillary NMIBC (cohort A, 102 patients) or papillary carcinoma only (cohort B, ongoing) were treated with pembrolizumab (200 mg IV every 3 wk) [43]. The total anticipated treatment duration was 24 mo, or until recurrence, progression, or unacceptable toxicity. All patients had an endoscopic evaluation at 3 mo, and those with the persistent high-grade disease were removed from the trial. The median treatment duration was 4.2 mo (IQR 3.4–9.1 mo), and a median of seven cycles (five to 14) was administered. A clinical complete response was observed in 39/96 (41%) after 12 wk. The median duration of response was 16 mo, and 18/39 (46%) had recurrence by 12 mo (19% of the overall cohort). Progression to MIBC, metastatic cancer, or death was observed in 9%, and a treatment-related Gr 3–4 adverse event occurred in 13%, but there were no treatment-related deaths. A total of 38 patients underwent RC, only three of whom had a pT3–4 stage, including two with pN1.

Pembrolizumab was approved by the FDA on January 2020 for patients with BCG-unresponsive CIS ± papillary carcinoma in patients who are ineligible for or who refuse RC. In a similar single-arm phase 2 trial design, S1605 tested atezolizumab in patients with BCG-unresponsive CIS ± papillary UC. At 3 mo, 20/74 (42%) achieved a complete clinical response and at 6 mo 27%; 49% of these responders were free of recurrence 12 mo later (18 mo after enrollment). The median duration of response was 15.4 mo. Five patients had progression to MIBC (three patients) or mUC (two patients). Gr 3–5 treatment-related adverse events occurred in 16% of patients, including two deaths from immune-related adverse events. While this trial showed similar outcomes to KEYNOTE-057, the study design set higher boundaries for efficacy and was therefore considered negative. The trial arm for patients with papillary disease only did not accrue completely. Trials evaluating CPIs in BCG-unresponsive patients are described in Table 4.

3.3.2. *BCG exposed*

BCG-exposed NMIBC is defined by high-risk NMIBC in patients who have received some BCG but do not meet the strict criteria of BCG-unresponsive NMIBC. KEYNOTE-676 (NCT03711032; arm A) is a phase 3 trial comparing BCG induction and maintenance to pembrolizumab and BCG induction and maintenance (dosed at 3 mo). In this trial, pembrolizumab is administered IV at 400 mg every 3 wk for up to nine doses. This trial is actively accruing. A similar trial with nivolumab and linrodostat mesylate (IDO1 inhibitor) closed early (NCT03519256).

3.3.3. *BCG naïve*

At the time of publication, two trials have been completed evaluating CPIs in BCG-naïve patients with NMIBC, but neither has been reported. Current trials evaluating CPIs in BCG-naïve patients are listed in Table 5. The largest study POTOMAC is a three-arm trial comparing BCG (arm C) with durvalumab and BCG induction with maintenance (arm A) to BCG induction only and durvalumab (arm B). Stratification includes high-risk papillary tumors and CIS, with a primary endpoint being DFS. POTOMAC is fully enrolled and conducted through Canada, Europe, and Asia with different strains of BCG. If successful, the use of different strains in POTOMAC may possibly impact regulatory approval of durvalumab for high-risk NMIBC in the USA. CREST (NCT04165317) is a similarly designed trial using the subcutaneously delivered sasanlimab (PF-06801591) given

Table 4 – Clinical trials in progress involving checkpoint immunotherapy in BCG-unresponsive patients

Trial	Phase	Arms	Patients	Outcome	clinicaltrials.gov	Estimated completion	Estimated study completion
POTOMAC	3	Durvalumab + BCG (I + M) vs durvalumab + BCG (induction only) vs BCG (I + M)	1018	DFS	NCT03528694		June 30, 2026
CREST	3	Sasanlimab + BCG (I + M) vs sasanlimab + BCG (induction only) vs BCG (I + M)	999	EFS	NCT04165317		December 23, 2026
Keynote-676-B	3	Pembrolizumab + BCG (I + reduced M) vs pembrolizumab + BCG (I + full M) vs BCG (I + M)	1525	EFS	NCT03711032		April 30, 2029
ALBAN	3	Atezolizumab + BCG (I + M) vs BCG (I + M)	516	RFS	NCT03799835		

BCG = bacillus Calmette-Guérin; DFS = disease-free survival; EFS = event-free survival; I = induction; M = maintenance; RFS = recurrence-free survival.
Columns include trial name (where available), agents tested, trial phase, number of patients, described primary outcomes, clinicaltrials.gov number, estimated completion, and study completion dates from clinicaltrials.gov.

Table 5 – Clinical trials in progress involving checkpoint immunotherapy in BCG-naive patients

Trial	Phase	Arms	Patients	Outcome	clinicaltrials.gov
Keynote-57B	2	Pembrolizumab	260	CRR, DFS	NCT02625961
Keynote-676A	3	Pembrolizumab + BCG (I + M) vs BCG (I + M) vs	1525	CCR	NCT03711032
S1605	2	Atezolizumab	202	CRR at 25 wk for Cis, EFS at 18 mo	NCT02844816
CORE-001	2	CG007 + pembrolizumab	37	CRR at 12 mo	NCT04387461
A031803	2	Pembrolizumab + gemcitabine	161	CRR at 6 mo (Cis), EFS at 18 mo	NCT04164082
SunRISe-1	2	TAR-200 + cetrelimab vs cetrelimab vs TAR-200	200	Overall CRR	NCT04640623
ADAPT-BLADDER	1/2	Durvalumab + BCG vs durvalumab + EBRT vs retreatment with BCG	186	RFS 6 mo	NCT03317158
PREVERT	2	Avelumab + EBRT + avelumab	67	High-risk RFS at 1 yr	NCT03950362

BCG = bacillus Calmette-Guérin; CCR = clinical complete response; Cis = cisplatin; CRR = complete response rate; DFS = disease-free survival; EBRT = external beam radiation therapy; EFS = event-free survival; I = induction; M = maintenance; RFS = recurrence-free survival.
Columns include trial name (where available), agents tested, trial phase, number of patients, described primary outcomes, clinicaltrials.gov number, estimated completion, and study completion dates from clinicaltrials.gov.

with BCG induction (arm B) or BCG induction and maintenance (arm A) compared with BCG alone (induction and maintenance). CREST has also completed accrual but has not yet reported. The ALBAN trial is testing atezolizumab in a similar trial that is actively enrolling in Europe.

4. Conclusions

The role of CPIs in 1L mUC has been well investigated and restricted to platinum-ineligible patients (pembrolizumab only) in the USA based on FDA approval. In Europe, both atezolizumab and pembrolizumab are approved for PD-L1–positive tumors that are cisplatin ineligible. Switch maintenance avelumab after no progression with chemotherapy is the current standard of care for 1L bladder cancer. While multiple trials investigate neoadjuvant CPIs, adjuvant nivolumab is associated with improved DFS in patients at a high risk of relapse and is FDA approved but with immature OS. In Europe, nivolumab is approved only for patients with PD-L1–positive tumors. While CPIs are approved for BCG-unresponsive CIS in the USA for patients who are not fit or who refuse RC, phase 3 trials of BCG-naïve and BCG-exposed NMIBC are pending. We anticipate more applications of combination therapies with CPIs across UC stages, while the prospective validation of promising biomarkers may help inform future patient selection and resistance mechanisms (Fig. 1).

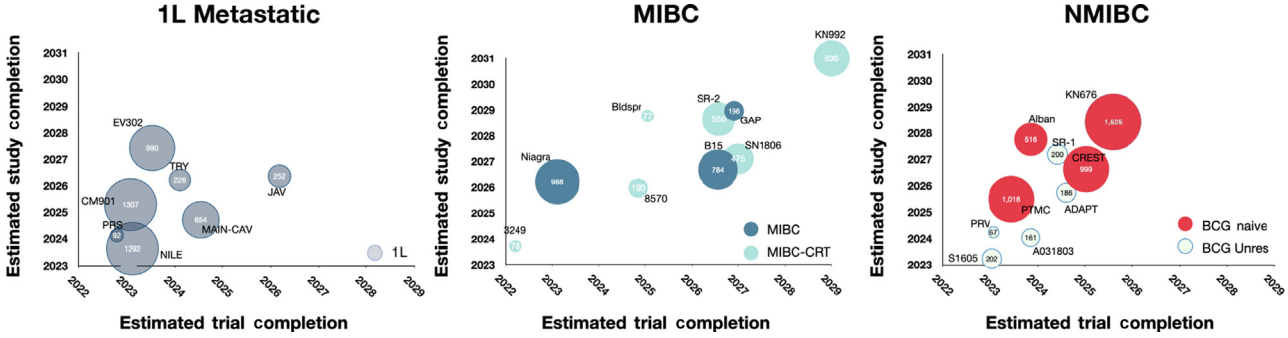

Fig. 1 – Timing of clinical trials in urothelial cancers including checkpoint immunotherapy. In each chart, the expected date of trial closure (*x* axis) is compared with the expected date of study completion (*y* axis). The area of each bubble is proportional to the expected enrollment in the trial. BCG = bacillus Calmette-Guérin; CRT = chemoradiotherapy; 1L = first line; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; BCG Unres = BCG unresponsive.

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