



# Combination therapies involving checkpoint-inhibitors for treatment of urothelial carcinoma: a narrative review

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**Abstract:** The implementation of immune checkpoint-inhibitors (CPI) has significantly improved the prognosis of a subgroup of patients with urothelial bladder cancer (BC). Still, the majority of patients will progress or experience a recurrence on CPI monotherapy. The next generation of clinical trials is now testing combination therapy with CPI and other agents that target different oncogenic mechanisms in an effort to improve efficacy. The beneficial toxicity profile of CPI but also the approval of CPI combinations in other cancer sites justifies their investigation also in BC. Here we report on clinical trials in muscle-invasive, locally advanced and metastatic BC combining CPI with other therapies, with a focus on the latest results presented at ASCO GU 2020, ASCO 2020 and ESMO 2019 as well as Phase-III trials currently ongoing. Multiple phase I-III clinical trials are investigating the combination of a CPI with a second CPI, with chemotherapy, or with targeted therapies like fibroblast growth factor receptor (FGFR) inhibitors or Nectin-4 inhibitors in different disease states. The results of more than 10 phase-III trials in advanced BC are eagerly awaited. Preliminary data are contradictory, as some trials released promising interim results, while others reported failure to achieve the primary endpoints. Taken together, combining CPI with other therapies is a logical and potentially promising approach, but it is too early to draw conclusions on specific combinations. As combinatorial therapies markedly increase the level of complexity, bedside-to-bench studies are warranted to gain deeper insight of underlying biological mechanisms which can be used to optimize future trials.

**Keywords:** Urothelial carcinoma; immunotherapy; chemotherapy; targeted therapy; antibody drug conjugate

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## Introduction

Radical cystectomy after neoadjuvant cisplatin-based chemotherapy is the standard therapy with curative intent for non-metastatic muscle-invasive bladder cancer (BC). Compared to other genitourinary cancers, the long-term survival rate is still poor for patients with advanced BC, mainly due to recurrences and metastatic spread (1). Before 2016, the recommended first-line therapy for locally advanced and metastatic urothelial carcinoma (mUC) was cisplatin-based chemotherapy, and there were

no established, efficacious second-line options. Although 60–70% of eligible patients respond to cisplatin, long-term survival is only approximately 15% (2,3).

Around 40 years after the successful introduction of immunotherapy for non-muscle-invasive BC in the form of intravesical Bacillus-Chalmette-Guerin (BCG) instillation, several programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) immune checkpoint inhibitors (CPI) have been approved for the first- and second-line setting in mUC. Regulatory approval has been granted for

the PD-1 inhibitors pembrolizumab and nivolumab and the PD-L1 inhibitors atezolizumab, avelumab and durvalumab in the United States, with more restricted approvals in other countries. Overall response rates (ORR) for CPI monotherapy range between 13% and 21% in unselected patient cohorts (4-11), and many of these responses are durable.

Undoubtedly, these CPI have revolutionized the treatment of mUC, with a subgroup of patients demonstrating sustained therapeutic responses. Nevertheless, progression and relapses occur in the majority of patients receiving CPI therapies. Intratumoral heterogeneity and the Darwinian selection of treatment-resistant tumor subclones, adaptive changes in tumor cells exposed to CPI, and alternative mechanisms of immune evasion have been proposed to be responsible for the failure of CPI monotherapy (12,13). Rational combination of CPI with other therapies might overcome resistance by simultaneously utilizing different modes of action and target molecules. The comparatively low rate of severe adverse events with CPI and the approval of CPI combinations in renal cell carcinoma and melanoma have given impetus to clinical trials testing CPI combination therapy in BC (14,15). In this review, we will discuss available preliminary data and highlight important phase III trials for several CPI combinations in muscle-invasive, locally advanced and metastatic BC. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1177>).

### Dual checkpoint inhibition

Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy demonstrated an absolute survival benefit of 5% to 8% compared to radical cystectomy alone (16). However, approximately half of patients is ineligible for cisplatin, due especially to impaired renal function and other co-morbidities. There are no alternative efficacious neoadjuvant therapies for this patient subpopulation.

The Phase Ib NABUCCO trial (NCT03387761) is investigating the combination of nivolumab and the CTLA4 (cytotoxic T-lymphocyte-associated Protein 4) inhibitor ipilimumab in the neoadjuvant setting in patients with stage III BC (cT3-4aN0M0 or  $\geq$  cT1N+M0) ineligible or unwilling to receive cisplatin-based neoadjuvant chemotherapy (Table 1). Primary and secondary endpoints were feasibility and pathologic complete response (pCR) rate, respectively. In a preliminary report 23 of the 24 patients enrolled underwent radical cystectomy within

12 weeks from the first cycle and 54% of patients experienced high-grade adverse events (17). A pCR rate of 45% (10/22) was reported for the whole cohort, which was higher in PD-L1 positive (60%) *vs.* negative patients (22%). In comparison, the single arm phase II monotherapy trials with atezolizumab (ABACUS) and pembrolizumab (PURE-01) reported pCR rates of 31% and 37%, respectively (18,19).

The combination of the two CPI nivolumab and ipilimumab is also under investigation in the Phase I/II CheckMate 032 (NCT01928394) multicenter study after platinum-based chemotherapy for mUC (20). The three arms were NIVO3 (nivolumab 3 mg/kg monotherapy q2w), NIVO3+IPI1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q3w for 4 cycles followed by nivolumab monotherapy 3 mg/kg q2w) and NIVO1+IPI3 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3w for 4 cycles followed by nivolumab monotherapy 3 mg/kg q2w). The primary endpoint was investigator-assessed ORR. Notably, the NIVO1+IPI3 arm was expanded with a protocol amendment and patients were included after the two other arms were closed. In an abstract report on this trial, 78, 104 and 92 patients were randomized into the NIVO3, NIVO3+IPI1 and NIVO1+IPI3 arms, respectively. In the NIVO3, NIVO3+IPI1 and NIVO1+IPI3 arms, the primary endpoint ORR was 25.6% (95% CI: 16.4–36.8%), 26.9% (95% CI: 18.7–36.5%) and 38.0% (95% CI: 28.1–48.8%). Notably, the extended follow-up data of the phase-III approval trial comparing pembrolizumab *vs.* chemotherapy as second-line treatment reported an ORR of 21.1% in the CPI arm, which is markedly lower compared to the ORR reported for the NIVO1+IPI3 arm in the CheckMate 032 study (4), as far as comparisons are possible across trials. Interestingly, in the NIVO1+IPI3 arm the ORR was 23.8% (95% CI: 12.1–39.5%) in patients with low PD-L1 expressing tumors (<1%) *vs.* 58.1% (95% CI: 39.1–75.5%) in patients with PD-L1 positive tumors. Treatment-related grade 3 and 4 adverse events occurred in 21 patients (26.9%) of the NIVO3 arm, 32 patients (30.8%) of the NIVO3+IPI1 arm and 36 patients (39.1%) of the NIVO1+IPI3 arm, indicating that the higher dose ipilimumab may increase toxicity. There was one treatment-related death in both the NIVO3 and the NIVO3+IPI1 arms. It is important to note that this study was not powered to compare between each of the arms nor to compare the ORR between patients stratified by PD-L1 expression.

The promising results of the Phase I/II CheckMate 32 study were the foundation for the ongoing CheckMate 901 Phase III trial (NCT03036098) which is comparing

Table 1 Clinical trials

Name	Category	Compounds	Setting	Phase	NCT	Results
ENERGIZE	CPI + Chemo	Nivolumab + chemo +/- IDO1-inhibition	NAC	III	NCT03661320	No
BLASST-1	CPI + Chemo	Nivolumab + chemo	NAC	II	NCT03294304	Yes
GU14-188	CPI + Chemo	Pembrolizumab+ chemo	NAC	Ib/II	NCT02365766	Yes
NABUCCO	CPI + CPI	Nivolumab + ipilimumab	NAC	Ib	NCT03387761	Yes
SAKK 06/17	CPI + Chemo	Durvalumab + chemo	Perioperative	II	NCT03406650	Yes
NIAGARA	CPI + Chemo	Durvalumab + chemo	Perioperative	III	NCT03732677	No
Keynote-866	CPI + Chemo	Pembrolizumab+ chemo	Perioperative	III	NCT03924856	No
IMvigor 130	CPI + Chemo	Atezolizumab + chemo	Metastasis, first-line	III	NCT02807636	Yes
CheckMate 901	CPI+CPI/CPI+ Chemo	Nivolumab + ipilimumab/ nivolumab + chemo	Metastasis, first-line	III	NCT03036098	No
DANUBE	CPI + CPI	Durvalumab + ipilimumab	Metastasis, first-line	III	NCT02516241	Yes
NILE	CPI +/- CPI + Chemo	Durvalumab +/- tremelimumab + chemo	Metastasis, first-line	III	NCT03682068	No
Keynote-361	CPI + Chemo	Pembrolizumab+ chemo	Metastasis, first-line	III	NCT02853305	Yes
PEANUT	CPI + Chemo	Pembrolizumab+ albumin-bound paclitaxel	Metastasis, first-line	II	NCT03464734	Yes
CheckMate 032	CPI + CPI	Nivolumab + ipilimumab	Metastasis, second-line	I/II	NCT01928394	Yes
FIERCE22	CPI + FGFR3	Pembrolizumab+ vofatamab	Metastasis, second-line	Ib/II	NCT03123055	Yes
EV-103	CPI + Nectin 4-inhibition	Pembrolizumab+ enfortumab-vedotin	Metastasis, first-line	Ib	NCT0328854	Yes
NORSE	CPI + panFGFR	Cetrelimab + erdafitinib	Metastasis, first-line	II	NCT03473743	Yes
EV-302	CPI + Nectin 4-inhibition +/- Chemo +/- platinum-based chemotherapy	Pembrolizumab + enfortumab vedotin	Metastasis, first-line	III	NCT04223856	No

Chemo, chemotherapy; CPI, checkpoint inhibitor; FGFR3, fibroblast growth factor receptor 3.

nivolumab + ipilimumab (NIVO1+IPI3) *vs.* nivolumab + standard of care (SoC) chemotherapy *vs.* SoC chemotherapy alone in both cisplatin-eligible and -ineligible patients with mUC who have received no prior systemic chemotherapy (21). The results of this Phase III trial are eagerly awaited and will answer the question whether dual CPI combination is superior to CPI monotherapy or CPI in combination with chemotherapy.

In a trial that is similar in design to the CheckMate 901 trial, the phase III DANUBE study (NCT02516241) randomized more than 1,000 patients to treatment with the combination of durvalumab and the CTLA-4 inhibitor tremelimumab *vs.* durvalumab alone *vs.* SoC chemotherapy in patients with mUC in the first-line setting. Both cisplatin-eligible and -ineligible patients were included. The primary endpoint for durvalumab monotherapy *vs.*

SoC chemotherapy was overall survival (OS) in patients with PD-L1 positive tumors. The co-primary endpoint for durvalumab + tremelimumab *vs.* SoC chemotherapy was OS in patients regardless of tumor PD-L1 status. The DANUBE trial failed to meet either primary endpoint. In the PD-L1 positive cohort, there was no difference in OS between durvalumab monotherapy *vs.* SoC chemotherapy (HR 0.89, 0.71–1.11,  $P=0.3039$ ). Furthermore, the combination of PD-L1 inhibition and CTLA4 inhibition did not outperform SoC chemotherapy (HR 0.85, 0.72–1.02,  $P=0.0751$ ) (22). The failure of this large trial once again underlines the obligation to conduct phase-III trials in order to validate results of earlier phase studies. This also reminds us that we have to be very cautious when predicting future directions based on early clinical trials. These lessons were reinforced with the results of the IMvigor 130 trial

described below.

### Checkpoint-inhibitors combined with chemotherapy

Cisplatin-based chemotherapy followed by CPI is the backbone of systemic therapy in mUC. Since both therapies have very different mechanisms of action, and since chemotherapy can potentially increase antigen presentation from tumors that could augment the effect of CPI, combining both therapies have been a logical next step in clinical trial design, with the anticipation that this might increase the number of patients who are able to achieve long-term disease control.

The phase II BLASST-1 (Bladder Cancer Signal Seeking Trial) study (NCT03294304) investigated neoadjuvant nivolumab together with the SoC gemcitabine and cisplatin in patients with muscle-invasive BC (cT2-T4a, N $\leq$ 1, M0). Primary and secondary endpoints were pathological response ( $\leq$ ypT1, N0) and safety as well as progression-free survival (PFS), respectively. The combination of CPI and chemotherapy was administered for 4 cycles followed by radical cystectomy within 8 weeks after the last systemic therapy. In a preliminary report based on all 41 patients enrolled, the primary endpoint was reached in 65.8% (27/41) (23). Grade 3 or 4 adverse events were observed in 20% of the patients and were largely attributed to the chemotherapy component. Neither delay of radical cystectomy nor unexpected surgical complications were observed. The preliminary results of this study are noteworthy, as the pathological response rate was higher than historical controls treated with neoadjuvant gemcitabine and cisplatin (24), although the difference in response rates to neoadjuvant MVAC is not vastly different (38.5% ypT0N0, down-staging rate not available) (25), and randomized trials will be necessary to show true superiority.

Building on the promising signal of the BLASST-1 trial, the ENERGIZE phase III study (NCT03661320) has been launched to investigate the combination of cisplatin-based neoadjuvant chemotherapy and nivolumab with or without the selective IDO1 (indoleamine 2,3-dioxygenase) inhibitor linrodostat mesylate (BMS-986205) (26). In this trial the CPI +/- IDO1 inhibitor therapy will continue post-operatively. This is one of the first trials to introduce triple therapy combinations including chemotherapy and CPI, and it suggests that triplet combinations with other targeted therapies are likely on the horizon.

Similar to BLASST-1, the single-arm phase II SAKK

06/17 trial (NCT03406650) investigated the combination of durvalumab and gemcitabine/cisplatin in the perioperative setting (27). An interim analysis revealed that 9 of 34 (26.5%) patients had pCR and 15 (44.1%) had ypT $\leq$ 1N0. Four patients who did not proceed to cystectomy were considered non-responders, which may artificially reduce apparent efficacy.

The GU14-188 trial (NCT02365766) is a third phase Ib/II trial investigating the combination of chemotherapy and CPI in the neoadjuvant setting in patients with cT2-4aN0M0 BC (28). Cohort 1 included cisplatin-eligible patients receiving 4 cycles of cisplatin, gemcitabine and pembrolizumab and cohort 2 included cisplatin-ineligible patients receiving 3 cycles of gemcitabine and pembrolizumab (29). Of 43 patients enrolled in cohort 1, 61.1% (95% CI: 0.45, 0.75) were down-staged to ypT $\leq$ 1N0 and 44.4% had a complete pathological response (ypT0N0). In cohort 2, 51.6% (95% CI: 0.35, 0.68) were ypT $\leq$ 1N0 and 45.2% were ypT0N0 at radical cystectomy. These response rates are particularly encouraging in cisplatin-ineligible patients who otherwise do not have options for neoadjuvant therapy, and they are higher than response rates reported for neoadjuvant CPI monotherapy (18,19). PD-L1 expression did not correlate with outcome in the GU14-188 study.

Based on these promising results, the phase III KEYNOTE-866 study (NCT03924856) is investigating perioperative pembrolizumab + chemotherapy *vs.* perioperative placebo + chemotherapy (27). Pembrolizumab will be continued for up to 13 3-week cycles after surgery. Patients with non-metastatic muscle-invasive BC (cT2-4aN0M0) are being enrolled. The co-primary endpoints will be pCR in all patients and in patients with PD-L1 positive tumors. OS, toxicity and pathological down-staging are secondary endpoints. The NIAGARA trial (NCT03732677) is a similar large open-label phase III trial in the same disease state that will randomize patients to neoadjuvant gemcitabine/cisplatin + perioperative durvalumab versus neoadjuvant gemcitabine/cisplatin alone (30).

In the metastatic setting, the IMvigor130 trial (NCT02807636) was the first phase III trial to report results from combined CPI and chemotherapy (11). This study included both cisplatin-eligible and -ineligible patients in the first-line. Patients were randomized into three arms: atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B) or placebo plus platinum-based chemotherapy (group C). The co-primary endpoints were PFS and OS comparing only group A

versus group C, with no comparisons planned with group B. The final PFS analysis and an interim OS analysis have been reported, with the final OS results pending. The trial enrolled 1,213 patients and the median follow-up was 11.8 months (IQR, 6.1–17.2). PFS was 8.2 months (95% CI: 6.5–8.3) in group A and 6.3 months (95% CI: 6.2–7.0) in group C (HR: 0.82, 95% CI: 0.70–0.96;  $P=0.007$ ), indicating superiority of the combination over chemotherapy alone. Interim OS was 16.0 months (13.9–18.9) in group A and 13.4 months (12.0–15.2) in group C (HR: 0.83, 95% CI: 0.69–1.00,  $P=0.027$ ) and therefore did not reach the prespecified level of significance ( $P=0.007$ ). Grade 3 and 4 adverse events were seen in 81%, 15% and 81% for group A, B and C, respectively. The ORR was similar between group A and group C (47% *vs.* 44%) although the rate of complete responses was greater in the combination arm (13% *vs.* 7%). Taken together, this study shows promising results for the combination of chemotherapy and CPI, but the final OS analysis will determine the true added value of combination therapy, since patients progressing on platinum-based chemotherapy in group C still have the option of receiving CPI as a second-line therapy, which could impact OS.

Two other large phase III trials, similar to IMvigor130, have investigated the combination of chemotherapy and CPI for first-line treatment of mUC (31). The NILE study (NCT03682068) has not yet completed accrual, and plans to randomize 1434 patients to durvalumab + SoC chemotherapy versus durvalumab + tremelimumab + SoC chemotherapy versus SoC chemotherapy alone (31). The KEYNOTE-361 trial (NCT02853305) has completed accrual, randomizing 1,010 patients to pembrolizumab + SoC chemotherapy versus pembrolizumab monotherapy versus SoC chemotherapy alone. Co-primary endpoints were PFS and OS in the intention to treat population. Initial results were presented at ESMO Virtual Congress 2020 (32). The prespecified level of statistical significance for both primary endpoints, PFS (HR 0.78, 9.65–0.93,  $P=0.0033$ ) and OS ( $P=0.86$ , 0.72–1.02,  $P=0.0407$ ), were not reached.

The modest results of IMvigor130 and the reported failure of KEYNOTE-361 to meet primary endpoints have tempered the enthusiasm for combined CPI and chemotherapy for first-line therapy of mUC, especially in light of the more pronounced OS benefit of switch maintenance avelumab after first-line platinum-chemotherapy in the JAVELIN Bladder 100 trial (NCT02603432) (33). It is possible that the same tumors respond to both CPI

and chemotherapy, so that the additive benefit is modest. Definitive conclusions cannot be drawn until complete trial results have been reported.

One phase II trial tested CPI plus chemo for second-line treatment of mUC. The PEANUT trial (NCT03464734) investigated the combination of pembrolizumab and nanoparticle albumin-bound paclitaxel (34). Seventy patients were enrolled and an encouraging ORR of 39% and CR of 14.3% were reported.

### Other combinatorial approaches including checkpoint-inhibitors

Combining CPI with other compounds is not limited to adding chemotherapy or another CPI. Two other drugs have been approved by the FDA for second- and third-line treatment of patients with mUC, and both are being tested in combination with CPI. The pan-FGFR inhibitor erdafitinib has demonstrated efficacy in a single arm phase II study for patients with specific alterations in FGFR2 and FGFR3 (35). In the NORSE trial (NCT03473743) combining erdafitinib plus cetrelimab, a newer PD-1 inhibitor, 5 of 7 patients (71%) demonstrated an objective response (36). This combination is now being tested in a randomized phase II trial for first-line management of cisplatin-ineligible patients with mUC (NCT03473743). In the second-line, post-platinum mUC setting, the Phase-Ib/II FIERCE22 trial (NCT03123055) tested the combination of pembrolizumab and a selective anti-FGFR3-antibody (vofatamab). This trial showed promising results on interim analysis with an ORR of 29.6% (37).

The antibody-drug conjugate enfortumab-vedotin targeting Nectin-4 was granted accelerated FDA approval based on the single arm phase II EV-201 trial, which showed an ORR of 44% including a CR of 12% in mUC patients previously treated with both platinum-based chemotherapy and CPI (38). Early results from the phase Ib EV-103 study (NCT03288545) testing the combination of pembrolizumab and enfortumab-vedotin for first-line treatment of 45 cisplatin-ineligible mUC patients demonstrated an ORR of 73.3% including a CR of 15.6%, and a disease-control rate of 93.3%, which is extraordinarily high compared to other compounds (39). EV-103 has sparked great interest in the corresponding phase III trial EV-302 (NCT04223856) which is randomizing patients with mUC to enfortumab plus pembrolizumab with or without platinum-based chemotherapy, versus chemotherapy alone.

Other drugs under investigation in combination with



CPI are PARP-inhibitors (NCT03459846), interleukin-2 agonists (NCT04209114) and multiple-kinase inhibitors (NCT03898180), among many others novel agents.

## Conclusions

Although CPI monotherapy leads to durable responses in a subgroup of patients, most patients with locally advanced and mUC still do not benefit. Progression under CPI is the rule, and further improvement of patient outcomes will likely depend on effective combination therapies that build on the success of CPI by simultaneously blocking independent oncologic pathways. Consequentially, there is much anticipation around the many clinical trials investigating these combinations, especially the large phase III studies that may be practice-changing. Most trials to date have published either no results or only preliminary results, and there have been some reports and press releases indicating that large phase III trials in the first-line mUC setting have failed to meet the targeted endpoints. It is therefore impossible currently to project the future role of CPI combined with other drugs without awaiting the results of the relevant trials. As the level of complexity increases exponentially with combinatorial therapies, a deeper understanding of underlying biologic mechanisms through bedside-to-bench studies is warranted, in addition to additional clinical trials. This concentrated effort should promote better outcomes for patients with urothelial carcinoma.

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