Editorial Commentary

Combination therapies targeting different aspects of tumor biology for patients with advanced urothelial carcinoma

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Introduction

Urothelial carcinoma (UC) originates from the urothelial lining renal pelvis, ureter, bladder, and urethra. Based on the report from Global Cancer Statistics 2020, bladder cancer is the 7th and 13th most frequent malignancy among men worldwide and those in Japan, respectively (1,2). Unresectable, metastatic, or advanced UC (aUC) is a progressive, poor prognostic disease with a median overall survival (OS) time of approximately 19–26 months following first-line (1L) platinum-based chemotherapy and subsequent administration of immune checkpoint inhibitors (ICIs) including anti-PD-1 and anti-PD-L1 antibodies (3-6). A substantial proportion of the population responds poorly to chemotherapy and ICIs, resulting in poor survival outcomes. Novel upfront drug combinations including ICIs, antibody-drug conjugates, and tyrosine kinase inhibitors (TKIs) are currently being tested in an attempt to overcome drug resistance and improve antitumor activity.

As reported by Matsubara *et al.* in a recent issue of *European Urology* and based on the results of the LEAP-011 trial, lenvatinib plus pembrolizumab was not more effective than was pembrolizumab alone as a 1L therapy for aUC (6). Pembrolizumab is an anti-PD-1 inhibitor that is currently used as a second-line therapy for patients with aUCs refractory to platinum-based chemotherapy [approved by the Pharmaceuticals and Medical Devices Agency in Japan, Food and Drug Administration (FDA) in the USA, and European Medicines Agency (EMA) in the European Union]. It is also used as a 1L therapy for platinum-ineligible patients with aUC (FDA-approved) and cisplatin-ineligible patients with aUCs expressing PD-L1 with a combined positive score ≥10 (EMA-approved). Lenvatinib is a TKI targeting vascular endothelial growth factors 1–3, fibroblast growth factor receptors (FGFRs) 1–4, platelet-derived growth factor receptor α, KIT, RET, and other tyrosine kinase receptors and oncoproteins (7). Preclinical studies have shown that lenvatinib decreases the number of tumor-associated macrophages in the tumor microenvironment, leading to increased immune activation (8).

Owing to its immunomodulatory activity, lenvatinib was expected to exert an additive or synergistic antitumor effect when co-administered with an ICI. In the phase 1b/2 study 111/KEYNOTE-146 clinical trial of aUC, previously treated patients who received pembrolizumab plus lenvatinib had an objective response rate (ORR) of 25% and a disease control rate of 70% (9). Moreover, the combination of pembrolizumab and lenvatinib showed promising antitumor activity against other solid tumors (9).

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Matsubara *et al.* hypothesized that this combination therapy would have favorable oncologic benefits, with an acceptable safety profile in a 1L setting for cisplatin-ineligible patients (6).

Results of the LEAP-011 trial

The LEAP-011 trial was a double-blind, multicenter randomized control trial (6). The main eligibility criteria were age ≥18 years, a histologically or cytologically confirmed diagnosis of aUC, measurable target tumor ≥1 as per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines, and no prior systemic chemotherapy for aUC. Patients with recurrence >12 months after completion of either neoadjuvant chemotherapy prior to radical surgery or adjuvant chemotherapy following radical surgery were permitted. Eligible cases had an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–2 and a PD-L1-positive tumor (combined positive score ≥10) and were cisplatin-ineligible or had an ECOG-PS score of 2 and were platinum-ineligible regardless of PD-L1 status. Progression-free survival (PFS) and OS were the dural primary outcomes; PFS was assessed according to the RECIST v1.1 guidelines by a blinded independent central review. ORR and safety were the secondary outcomes.

A total of 487 patients were randomly administered intravenous pembrolizumab plus oral lenvatinib (combination arm, 245 patients) or pembrolizumab plus placebo (pembrolizumab arm, 242 patients). Lenvatinib 20 mg as the initial dose or placebo was administered orally once a day. In both arms, intravenous pembrolizumab 200 mg was administered once every 3 weeks for up to 35 times, corresponding to about 24 months, until disease progression was observed radiographically, patients experienced intolerable side effects, or physicians or patients decided to withdraw from the clinical trial. In case that one drug in the combination group was discontinued, the other drug could be continued. In the combination group, patients were treated with pembrolizumab a median of 5 cycles (interquartile range, 3–11 cycles) and lenvatinib 19.6 mg/day (interquartile range, 15–20 mg/day). In the pembrolizumab monotherapy group, patients were treated with pembrolizumab a median of 5 cycles (3–12 cycles). The median time of PFS of the combination group and pembrolizumab monotherapy group was 4.5 and 4.0 months [hazard ratio (HR) =0.90], respectively, while the median time of OS was 11.8 and 12.9 months (HR =1.14), respectively (*Figure 1*). The ORR was 33% [complete response (CR), 7.4%; partial response, 21%] and 29% (CR, 6.1%; partial response, 27%) in the combination and pembrolizumab arms, respectively.

Of 245 patients in the combination group, 211 (86%) had treatment-related adverse events (TRAEs), while 167 (69%) out of 242 patients in the pembrolizumab group had TRAEs. Grade ≥3 TRAEs were reported in 123 patients (50%) and 66 patients (27%), respectively. Forty-eight cases (20%) in the combination group and 22 cases (9%) in the pembrolizumab group discontinued treatment owing to a TRAE. Six and one treatment-related deaths were observed in the combination and pembrolizumab arms, respectively. The most frequently observed relevant AEs of any grade were proteinuria (41%), hypertension (41%), and hypothyroidism (37%) in the combination arm and proteinuria (25%), hypothyroidism (8.7%), and hematuria (12%) in the pembrolizumab arm. The safety profile of each drug was consistent with previously reported results (10,11).

Based on these findings, Matsubara *et al.* concluded that the balance between benefit and risk of the combination therapy was not superior to the pembrolizumab alone in patients with aUC in an IL setting (6). An external data monitoring committee recommended earlier termination of LEAP-011 trial than was initially planned.

Other clinical trials of 1L combination therapy for aUC

Table 1 lists several clinical trials investigating novel 1L combination therapies for patients with aUC with different backgrounds (e.g., cisplatin-eligible, platinum-eligible, cisplatin-ineligible, and platinum-ineligible) (6,12-22). The development of these therapies coincided with the accumulation of knowledge of the pathogenesis and genetic alterations of UC. Among the different types of therapeutic agents, TKIs such as lenvatinib and erdafitinib potentially play a vital role in current aUC treatment (23). In 2019, the FDA granted accelerated approval of erdafitinib for treatment of aUCs with susceptible *FGFR3* or *FGFR2* genetic alterations and progression during or following platinum-based chemotherapy. Moreover, a phase 1b/2 clinical trial (NORSE) concluded that erdafitinib plus cetrelimab (a PD-L1 inhibitor) was safe for further evaluation in patients with *FGFR2/3* alterations and aUC progression after at least one line of treatment (24). This combination is further being investigated in a randomized phase 2 clinical trial (NCT03473743).

In the CheckMate-901 trial, the combination of two

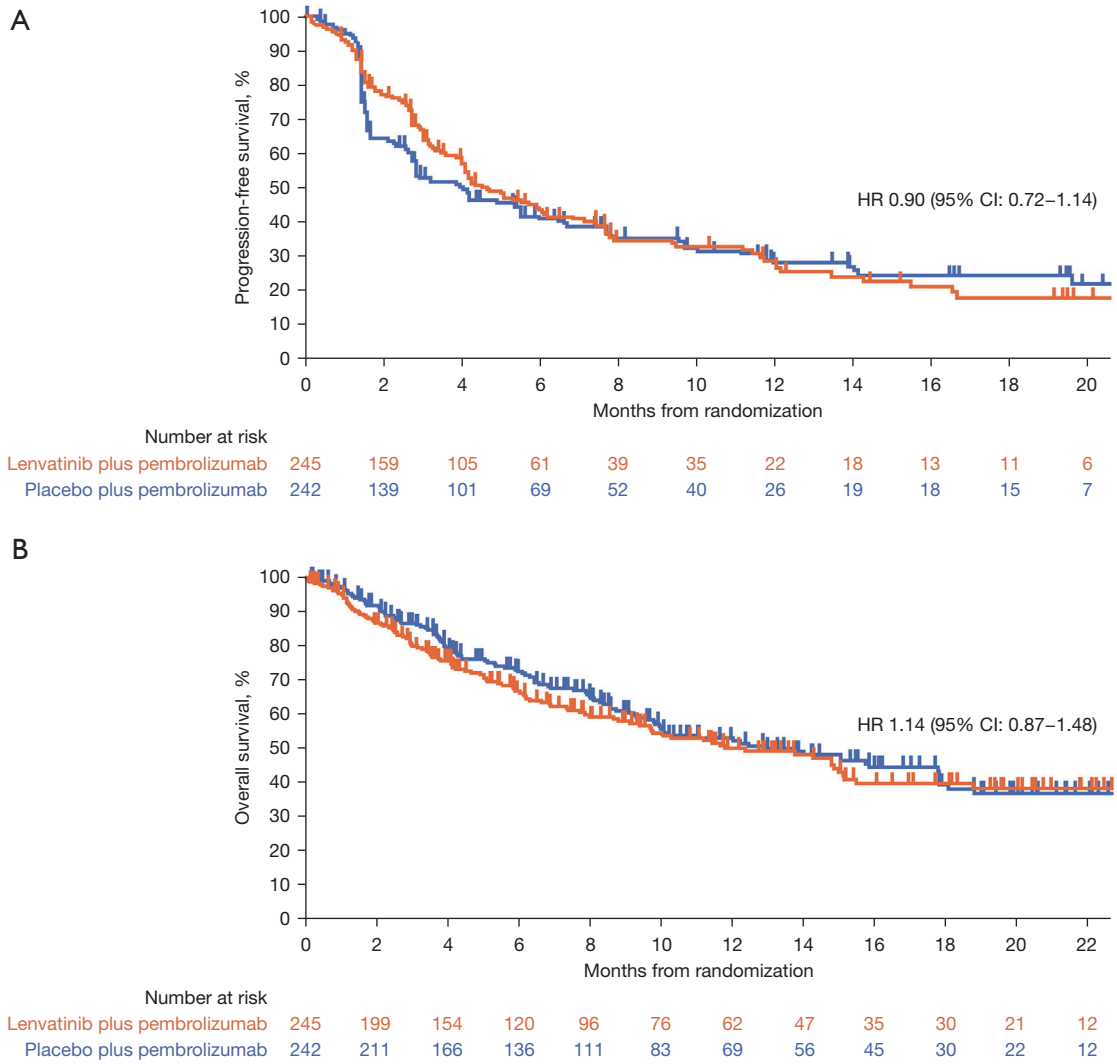

Figure 1 Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in the intention-to-treat population of the LEAP-011 clinical trial. The image has obtained permission from Elsevier (6). HR, hazard ratio; CI, confidence interval.

ICIs (ipilimumab and nivolumab) did not prolong OS compared with gemcitabine-cisplatin (GC) or gemcitabine-carboplatin (GCarbo) chemotherapy in patients whose tumors expressed ≥1% PD-L1 (16). However, in a subgroup analysis of cisplatin-eligible patients, GC chemotherapy with nivolumab better improved the outcomes of patients with previously untreated aUCs than did GC chemotherapy alone [HR for death, 0.78; 95% confidence interval (CI): 0.63–0.96; P=0.02]; the median survival time was 21.7 months (95% CI: 18.6–26.4) for the combination compared with 18.9 months (95% CI: 14.7–22.4) for chemotherapy alone (15). Of note, the median duration of CR was 37.1 months with GC chemotherapy with nivolumab and 13.2 months with GC alone. This result was one of the major highlights showing potential durable benefit in the combination. This clinical trial provided the first documentation of the survival benefit of combined ICI administration and standard chemotherapy; no survival benefits were observed in the IMvigor130 trial (atezolizumab) (13) and KEYNOTE-361 (pembrolizumab) (14) trials. The phase 3 NILE trial is currently investigating the efficacy of platinum-based chemotherapy plus durvalumab against human PD-L1 and tremelimumab against human CTLA-4) for previously untreated aUC (18).

The striking results of the EV-302 trial were presented

Table 1 Representative clinical trials with 1L combination therapies targeting different aspects of tumor biology for patients with advanced urothelial carcinoma

Reference	Type of combination	Trial phase; design	Trial ID; trial name	Interventions	Primary endpoint	Status[#] (last update posted)	No. of participants[#]	Results and interpretations
(6)	ICI + TKI	3; RCT	NCT03898180; LEAP-011	Arm A: pembrolizumab + lenvatinib Arm B: pembrolizumab + placebo	OS, PFS	Active, not recruiting (October 2023)	487 (actual)	The benefit-to-risk ratio for 1L lenvatinib plus pembrolizumab was not considered favorable as compared to pembrolizumab alone as 1L therapy in patients with aUC
(12)	TKI + ICI	1b/2; RCT	NCT03473743; NORSE	Phase 1b: erdafitinib + cetrelimab + cisplatin or carboplatin Phase 2, arm A: erdafitinib alone Phase 2, arm B: erdafitinib + cetrelimab	Phase 1b: DLT; phase 2: ORR and TEAE	Active, not recruiting (October 2023)	125 (actual)	Combination erdafitinib plus cetrelimab demonstrated clinically meaningful activity and was well tolerated. These results, in 1L cisplatin-ineligible patients, support activity of erdafitinib monotherapy in aUC with FGFR alteration
(13)	ICI + chemotherapy	3; RCT	NCT02807636; IMvigor130	Arm A: atezolizumab + GC or GCarbo Arm B: atezolizumab monotherapy Arm C: GC or GCarbo	OS, PFS	Active, not recruiting (June 2023)	1,213 (actual)	PFS: arm A =8.2 months, arm C =6.3 months OS: arm A =16 months, arm C =13.4 months Addition of atezolizumab did not impact OS, regardless of response to induction chemotherapy
(14)	ICI + chemotherapy	3; RCT	NCT02853305; KEYNOTE-361	Arm A: pembrolizumab + GC or GCarbo Arm B: pembrolizumab monotherapy Arm C: GC or GCarbo	OS, PFS	Completed (September 2023)	1,010 (actual)	Addition of pembrolizumab to 1L platinum-based chemotherapy did not significantly improve efficacy and should not be widely adopted for treatment of aUC
(15)	ICI + chemotherapy	3; RCT	NCT03036098; CheckMate901	Arm A: nivolumab + GC Arm B: GC	OS, PFS	Active, not recruiting (November 2023)	608 (actual)	Combination therapy with nivolumab plus gemcitabine-cisplatin resulted in significantly better outcomes in patients with previously untreated advanced urothelial carcinoma than gemcitabine-cisplatin alone
(16)	ICI combination	3; RCT	NCT03036098; CheckMate901	Arm A: nivolumab + ipilimumab Arm B: GC or GCarbo	OS in patients who are cisplatin-ineligible or who have a tumor PD-L1 expression of 1% or more & PFS in those who are cisplatin ineligible	Completed	707 (actual)	1L nivolumab/ipilimumab fails to improve OS *vs*. standard-of-care chemotherapy in patients with aUC
(17)	ICI combination	3; RCT	NCT02516241; DANUBE	Arm A: durvalumab + tremelimumab Arm B: durvalumab monotherapy Arm C: GC or GCarbo	OS in full analysis set and in PD-L1-high analysis set	Active, not recruiting (September 2023)	1,126 (actual)	This study did not meet either of its coprimary endpoints
(18)	ICI combination	3; RCT	NCT03682068; NILE	Arm A: durvalumab + GC or GCarbo Arm B: durvalumab + tremelimumab + GC or GCarbo Arm C: GC or GCarbo	OS	Recruiting (November 2023)	1,292 (estimated)	Ongoing, results not reported
(19)	ICI + ADC	3; RCT	NCT04223856; LBA6 EV-302/ KEYNOTE-A39	Arm A: pembrolizumab + EV Arm B: GC or GCarbo	OS, PFS	Recruiting (November 2023)	990 (estimated)	Pembrolizumab plus EV significantly improved outcomes in patients with previously untreated aUC, nearly doubling the median PFS and OS as compared to standard chemotherapy. The safety profile was generally manageable with no new safety signals
(20)	ICI + PARP inhibitor	2; RCT	NCT03459846; BAYOU	Arm A: durvalumab + placebo Arm B: durvalumab + olaparib	PFS	Active, not recruiting (September 2023)	154 (actual)	Adding olaparib to durvalumab did not improve survival outcomes in platinum-ineligible patients with aUC
(21)	1L chemotherapy followed by maintenance ICI + TKI	3; RCT	NCT05092958; MAIN-CAV Study	Arm A: maintenance avelumab alone Arm B: maintenance avelumab + cabozantinib	OS	Recruiting (November 2023)	654 (estimated)	Ongoing, results not reported
(22)	1L chemotherapy followed by maintenance ICI + ADC or other immunotherapy	2; RCT	NCT05327530; JAVELIN Bladder Medley	Arm A: maintenance avelumab Arm B: maintenance avelumab + sacituzumab govitecan Arm C: maintenance avelumab + M6223 Arm C: maintenance avelumab + NKTR-255	PFS, TEAE, AESI	Recruiting (October 2023)	252 (estimated)	Ongoing, results not reported

M6223 = anti-T cell-immuno-receptor with Ig and ITM domains (anti-TIGIT); NKTR-255 = interleukin-15 receptor agonist. [#], the data are based on the ClinicalTrials.gov (https://clinicaltrials.gov/). The 'estimated' enrollment indicates the target number of participants that the researchers need for the study. 1L, first line; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate; PARP, poly(ADP-ribose) polymerases; RCT, randomized controlled trial; GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; OS, overall survival; PFS, progression-free survival; DLT, dose limiting toxicity; ORR, objective response rate; TEAE, treatment emergent adverse event; AESI, adverse events of special interest; aUC, advanced/unresectable/metastatic urothelial carcinoma; FGFR, fibroblast growth factor receptor; EV, enfortumab vedotin.

by Powles *et al.* at the European Society for Medical Oncology (EMSO) Congress, which took place in Madrid, Spain on October 20–24, 2023 (19). This global, open-label, randomized phase 3 trial compared the efficacy of enfortumab vedotin (EV, an antibody-drug conjugate) plus pembrolizumab (experimental arm) with standard chemotherapy (control arm) in patients with previously untreated aUC. Importantly, an amendment to this trial allowed switch maintenance therapy with avelumab after induction chemotherapy with GC or GCarbo in the control arm, as is customary in contemporary real-world clinical practice. Patients in the experimental arm received 1.25 mg/kg of EV on days 1 and 8 and 200 mg of pembrolizumab on day 1 of each 3-week cycle. The primary endpoints were radiographic PFS and OS, and the secondary endpoints were ORR and safety.

The 886 patients in the EV-302 study were randomized into an experimental (442 patients) or control (444 patients) group; the median follow-up period was 17.2 months. Compared with standard chemotherapy, EV plus pembrolizumab significantly prolonged PFS (median PFS, 12.5 and 6.3 months, respectively; HR, 0.45; 95% CI: 0.38–0.54; P<0.001) and OS (median OS, 31.5 and 16.1 months, respectively; HR, 0.47; 95% CI: 0.38–0.58; P<0.001); by doing so, it reduced the risk of progression or death by 55% and the risk of death by 53%. The ORR was 67.7% in the experimental arm and 44.4% in the control arm (P<0.01). Grade ≥3 TRAEs were observed in 55.9% and 69.5% of the patients in the experimental and control arms, respectively. The most common grade ≥3 treatment-emergent AEs of interest in the experimental arm included severe skin reactions (11.8%). Powles *et al.* concluded that EV plus pembrolizumab provided a survival benefit, nearly doubling the PFS and OS times over those of standard chemotherapy (19). These impactful results support the use of this novel combination as an IL standard-of-care treatment for aUC.

1L chemotherapy with GC, GCarbo, or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (DD-MVAC), followed by switch maintenance avelumab or second-line pembrolizumab has been recommended in clinical practice guidelines for years. Based on the positive result of clinical trials, EV plus pembrolizumab and/or GC plus nivolumab would be widely accepted as the gold standard 1L treatment for patients with aUC in near future. However, treatment options should be selected with caution on a case-by-case basis. For example, elderly patients, vulnerable patients, or those with comorbidities are generally intolerant to intensified treatments and have high risk of treatment-related death. Still, vintage sequential therapy (chemotherapy followed by ICI) could play important roles in the real clinical setting.

Emerging 1L combination therapy of TKI plus immune oncology (IO) for cisplatin-ineligible aUC

Treatment options for cisplatin-ineligible and, particularly, platinum-ineligible patients with aUC are limited. The result of PemCab phase II trial 'Cabozantinib plus Pembrolizumab as First-line Therapy for Cisplatin-ineligible Advanced Urothelial Carcinoma' as presented by in the 2024 American Society of Clinical Oncology Genitourinary (ASCO GU) cancers symposium (25). In 36 patients with aUC who were cisplatin-ineligible or who refused cisplatin, a promising ORR of 45.7%, CR rate of 14.2%, and median duration of response of 14.7 months was observed for pembrolizumab plus cabozantinib as 1L therapy. The median number of cycles received were 10 cycles of pembrolizumab and 7.5 cycles of cabozantinib. With a median follow-up of 14.3 months, the median PFS and OS were 7.6 and 17.1 months, respectively. Moreover, zanzalintinib (XL092) is a next-generation TKI that inhibits cancer growth and spread through including VEGF receptors, MET, AXL and MER, which are common in those of cabozantinib (26). Thus, zanzalintinib might be a vital direction of clinical investigation to improve the therapeutic index. The potential of combination of cabozantinib/zanzalintinib and pembrolizumab should be further evaluated.

Summary

Advances in the understanding of the pathogenesis, biological characteristics, and genetic alterations of malignant diseases have led to the development of new drugs that target different aspects of aUC biology. Still, radical cure is not possible in the vast majority of patients with aUC, thus, further translational researches and clinical trials are definitely needed. Novel drugs and targets are being researched and will revolutionize the therapeutic landscape of UC.

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