Review Article

Immunotherapy for advanced urothelial carcinoma (UC): rational and current evidence

Mario Uccello[1], Sola Adeleke[2,3], Michele Moschetta[4], Aruni Ghose[5,6,7], Stergios Boussios[3,5,8,9]

[1]Department of Medical Oncology, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [2]Department of Oncology, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [3]Faculty of Life Sciences & Medicine, School of Cancer & Pharmaceutical Sciences, King's College London, London, UK; [4]Novartis Institutes for BioMedical Research, Basel, Switzerland; [5]Department of Medical Oncology, Medway NHS Foundation Trust, Gillingham, Kent, UK; [6]Department of Medical Oncology, Mount Vernon Cancer Centre, East and North Hertfordshire NHS Trust, London, UK; [7]Department of Medical Oncology, Barts Cancer Centre, St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [8]Kent Medway Medical School, University of Kent, Canterbury, UK; [9]AELIA Organization, Thessaloniki, Greece

Contributions: (I) Conception and design: M Uccello, M Moschetta, S Boussios; (II) Administrative support: S Boussios; (III) Provision of study materials or patients: M Uccello, S Adeleke; (IV) Collection and assembly of data: M Uccello, S Adeleke; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Mario Uccello. Department of Medical Oncology, University Hospital Southampton NHS Foundation trust, University Road, Southampton SO17 1BJ, UK. Email: mario_uccello@hotmail.it.

Abstract: Combination platinum-based chemotherapy has been the standard of care for several decades in first-line treatment of advanced urothelial carcinoma (UC) patients. UC is often chemosensitive, though durable responses are quite rare and the development of chemoresistance still leads to poor clinical outcomes. Up until a few years ago, UC patients could not benefit from any valuable alternatives to cytotoxic chemotherapy, but the scenario has been recently transformed by the advent of immunotherapy. Molecular biology of UC is characterised by a relatively high prevalence of alterations in DNA damage response pathway, genomic instability, high tumour burden, and elevated programmed cell death ligand 1 (PD-L1) protein expression, which are established factors predicting favourable response to immune checkpoint inhibitors (ICIs) in several tumour types. To date, various ICIs have been approved as systemic anti-cancer therapy for advanced UC in multiple settings, including first-line, maintenance, and second-line therapy. ICIs are also in development either as monotherapy or in combination with chemotherapy or other targeted agents. Moreover, a number of alternative ICIs, interleukins, and novel immune molecules have been identified as promising agents in advanced UC. Herein, we review rational and current literature evidence supporting the clinical development and current indications of immunotherapy, particularly focusing on ICIs.

Keywords: Urothelial carcinoma; bladder cancer; immunotherapy; immune checkpoint inhibitors (ICIs)

Submitted Nov 26, 2022. Accepted for publication May 12, 2023. Published online May 25, 2023.
doi: 10.21037/apm-22-1350
View this article at: https://dx.doi.org/10.21037/apm-22-1350

Introduction

Background

The chemotherapeutic management of patients with advanced urothelial carcinoma (UC) has changed little over the last 20 years. Platinum-based doublets remain the standard of care in the first-line setting. Although chemotherapy has relatively high level of activity, most patients will ultimately progress within 9 months of therapy, with median survival slightly exceeding 12 months with cisplatin-based combinations. Shorter survival of around 9 to 10 months has been reported in cisplatin-ineligible subjects treated with carboplatin-based chemotherapy (1,2). The underlying mechanisms of platinum resistance

are multifactorial and complex, involving expression of molecules involved in cisplatin transport and detoxification, increased DNA repair, and reduced apoptosis (3). Single agent taxanes or vinflunine have exhibited modest clinical activity and were previously the standard salvage systemic therapy in advanced UC (4). In the era of precision medicine, multiple targeted therapies have been successfully evaluated in advanced UC. Following the results of the phase 3 EV-301 trial, the antibody drug conjugate enfortumab vedotin has been approved for advanced UC patients who received a prior platinum-containing chemotherapy and an immune checkpoint inhibitor (ICI) (5). The recent approval of erdafitinib and the emergence of other potent and selective fibroblast growth factor receptor (FGFR) inhibitors has led to treatment improvement in advanced UC tumours harbouring FGFR3 or FGFR2 gene mutations (6).

Objective

In this review, we will focus on the rapid emergence of ICIs in the frontline and salvage therapy of advanced UC, particularly the anti-programmed cell death protein 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) inhibitors.

Rational for immunotherapy in advanced UC

UC of the bladder has long been known to be immune-responsive, with intravesical instillation of the Bacillus Calmette-Guerin (BCG) inducing cytotoxic T lymphocytes (CTLs) infiltration and promoting cell-mediated cytotoxicity against bladder tumour cells in subjects with non-muscle invasive bladder cancer. Despite decades of research and clinical use, the mechanisms of BCG-induced immunotherapeutic effect have not been fully clarified due to the complexity of the multiple biological aspects involved, including the innate and adaptive immune systems (7). An effective anti-tumour immune response comprises a series of events: (I) release of tumour antigens from damaged or dying cancer cells; (II) uptake and presentation of these antigens by dendritic cells and other antigen-presenting cells; (III) priming and activation of T cells; (IV) trafficking, infiltration and enrichment of T lymphocytes and natural killer (NK) cells; (V) recognition and killing of cancer cell by CTLs and NK cells (8). This cycle provides a valid backbone for understanding the mechanisms of response and resistance to immunotherapy. For instance, therapeutic cancer vaccines and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibodies work by priming, activating, and expanding T cells, whereas ICIs such as anti-PD-1/PD-L1 monoclonal antibodies restore T-cell function against cancer cells, primarily blocking the interaction with the PD-L1 on the tumour cell, thus inhibiting immune escape and tumour growth (9). Apart from breast, ovarian and prostate cancer, DNA damage response alterations are also quite common in UC and have been extensively studied as potential predictive factors of response to cisplatin, but they are also likely to play a role in the response to immunotherapeutic agents (10-12). Tumour mutational burden (TMB) has been recognised as a predictive biomarker for response to immune therapy in various cancer types. UC exhibits a high degree of TMB in comparison with the majority of other solid malignancies, suggesting promising potential for the development of immunotherapeutic agents in UC (13). High PD-L1 protein expression in tumour cells and/or tumour infiltrating cells is associated with better treatment response to ICIs in a number of tumour types, including UC. Indeed, PD-L1 is the sole biomarker extensively adopted and validated in clinical practice to guide treatment decisions regarding the use of ICIs in the management of UC (14). The value of PD-L1 has been highlighted by the restriction of the indication of anti-PD-1/PD-L1 agents to UC first-line patients with high level of PD-L1 expression. Nevertheless, the predictive value of PD-L1 expression is quite limited, which may be partially due to the dynamic expression and heterogeneity within the tumour microenvironment (14-16). For instance, there seems to be high degree of discordance in PD-L1 expression between primary and metastatic UC lesions (16). The accuracy of PD-L1 as a predictive factor of response to ICIs has been studied in several cancer types adopting different PD-L1 diagnostic assays, antibodies, scoring algorithms, and cut-offs to measure PD-L1 expression in either tumour cells, immune cells or both, thus leading to some variability in results (15). Further studies are warranted to develop a reliable predictive model using PD-L1 expression and other biomarkers in UC. In addition to the benefit provided by ICIs and other immunotherapy agents in terms of efficacy outcomes, the increased quality of life in cancer patients receiving immunotherapy is usually higher than in those treated with standard cytotoxic chemotherapy, thus reinforcing the rational for the clinical implementation of immunotherapy drugs in advanced UC (17).

Incorporation of ICIs into first-line and maintenance therapy in UC

ICIs are now a standard of care in first-line UC for cisplatin-ineligible patients. The phase II KEYNOTE-052 trial (18) investigated pembrolizumab as first-line therapy in 370 advanced UC patients who were ineligible for cisplatin-based chemotherapy. Encouraging findings from the updated analysis of this study showed an overall response rate (ORR) of around 28.6%, with around 5% of patients experiencing complete response (CR), and a median overall survival (OS) of 11.3 months (19). The safety data were comparable with the known safety profile of pembrolizumab, with around 15–20% Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 treatment-related adverse events (19,20). However, pembrolizumab was not found to improve OS in the phase III KEYNOTE-361 trial (2), which randomised around 1,000 first-line advanced UC patients to receive treatment with either pembrolizumab monotherapy, pembrolizumab plus platinum-based chemotherapy, or chemotherapy alone. After a median follow-up of 31.6 months, the median OS was quite similar among the three arms, reaching 15.6, 17.0, and 14.3 months, respectively. Similar data were published for atezolizumab in first-line advanced UC. The phase II IMvigor210 trial (21) evaluated atezolizumab in 119 advanced UC patients who were ineligible for cisplatin-based chemotherapy. The results from this study showed an ORR of 23%, with 9% of patients showing CR. Once again, the initial enthusiasm was hampered by the phase III trial data. In the IMvigor130 multicentre, phase III trial (20), untreated adult patients with advanced UC were randomly assigned to receive atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B), or placebo plus platinum-based chemotherapy (group C). Preliminary median OS was 16.0 months in group A, 15.7 months in group B, and 13.1 months in group C. Updated interim analysis showed numerical but not statistical median OS advantage for atezolizumab monotherapy (22). In 2018, the Food and Drug Administration (FDA) issued a safety notice for the use of first-line pembrolizumab and atezolizumab, warning that decreased survival from the use of these agents in comparison with platinum-based chemotherapy was found in preliminary analysis of the two phase III trials (KEYNOTE-361 and IMvigor130). Therefore, the FDA prescribing information of atezolizumab and pembrolizumab was restricted to cisplatin ineligible patients with high PD-L1 expression or patients ineligible to any platinum-based therapy (either cisplatin or carboplatin), regardless of PD-L1 status (23). Specific PD-L1 expression scores have been developed and implemented to better identify patients eligible to such agents. Differences in antibodies used, implemented platforms and testing algorithms have raised questions about interchangeability and comparability among these assays and their diagnostic applicability. However, PD-L1 expression remains crucial in selecting first-line patients and remains the only factor widely adopted to predict clinical benefit from ICIs in advanced UC (14,15). According to European Medicine Agency (EMA) and the National Institute for Health and Care Excellence (NICE), pembrolizumab and atezolizumab are currently approved as monotherapies for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥10 or tumour-infiltrating immune cells score (IC) ≥5, respectively (24,25). Several other trials have been investigating ICIs as first-line therapy for advanced UC given as monotherapy or combination, but so far there have been no trials showing clear superiority over cisplatinum-based standard therapy. In the DANUBE phase III trial (26), durvalumab monotherapy or in combination with tremelimumab failed to show increased survival when compared with standard of care platinum-based chemotherapy in untreated advanced UC patients. Similarly, the combination of nivolumab and ipilimumab did not improve OS versus standard chemotherapy in the front-line setting for patients with advanced UC whose tumor cells express PD-L1 ≥1%, according to findings from the CheckMate-901 trial (27). In the KEYNOTE-361 trial mentioned above (2), pembrolizumab in combination with chemotherapy failed to show a survival benefit in comparison with standard chemotherapy. Despite the initial activity often observed with platinum-based chemotherapy, most advanced UC patients will ultimately experience disease progression, with the majority of them being unable to receive second-line anti-cancer therapy due to clinical deterioration (28,29). Immunotherapy given as maintenance would increase the chance of advanced UC patients to receive clinical benefit from additional treatment while still retaining good performance status. In the phase III, multicentre, double-blind, controlled JAVELIN Bladder 100 clinical trial (30), 700 advanced or metastatic UC patients who did not have progressive disease following platinum-based first-line treatment, were randomly assigned to receive either maintenance avelumab

or best supportive care. Avelumab was administered at a dose of 10 mg per kilogram of body weight intravenously every 2 weeks. Infusion-related reactions are reported in up to 30% of patients treated with avelumab, which is higher than the rate usually reported with other ICIs. Therefore, antihistamine and acetaminophen were administered approximately 30 to 60 minutes before at least the first four infusions. The primary objective of the study was to assess whether avelumab maintenance would increase OS in both the overall population and among patients with PD-L1 positive expressing tumours. Progression-free survival (PFS), ORR and other efficacy outcomes were selected as secondary endpoints. In the overall population, OS was significantly longer in patients treated with avelumab (median OS 21.4 *vs.* 14.3 months; P=0.001). The survival benefit was maintained among patients with PD-L1 negative tumours and all the other protocol-specified subgroups. PFS was also longer in the experimental arm, when compared with the control group (median PFS 3.7 *vs.* 2.0 months; P<0.05). The safety profile was manageable and comparable with the known characteristics of ICIs. Fatigue, pruritus, diarrhoea, hypothyroidism, skin rash and infusion-related reactions were the adverse events more frequently attributable to avelumab. Taken together, these data support the adoption of avelumab maintenance as a standard of care in advanced UC patients whose disease has not progressed on first-line platinum-based therapy. Overall, PD-L1 or PD-1 inhibitor monotherapy has been incorporated into the standard of care of first-line UC or maintenance, whereas these agents have so far not provided additional positive results when combined with either chemotherapy or CTLA-4 inhibitors (23,24). It is unclear whether different PD-1 or PD-L1 inhibitors are entirely comparable in terms of efficacy, as no trials comparing efficacy among these agents exist. Metanalyses and indirect comparisons from clinical trials including patients with multiple tumour types may suggest some superiority in terms of PFS and OS for PD-1 inhibitors when compared to PD-L1 inhibitors (31). However, there are no valuable data supporting similar conclusion specifically to the UC population.

ICIs as second-line therapy in UC

UC patients progressing to first-line treatment have particularly poor prognosis and limited treatment options. Non-platinum chemotherapies given as monotherapies, such as taxanes or vinflunine, have been the standard of care before the approval of immunotherapy. Previous real-world data suggested that best supportive care was actually a very commonly adopted approach for second-line treatment in UC (28,29). ICIs have recently redefined the treatment landscape in this setting, as capable of providing patients with slightly longer median OS than chemotherapy and median duration of responses exceeding 12 months in UC patients experiencing partial response (PR) or CR (24). In the KEYNOTE-045 phase III trial (32), 542 advanced UC patients progressing after first-line platinum-based chemotherapy were assigned to receive either pembrolizumab or the physician's choice of second-line chemotherapy with paclitaxel, docetaxel or vinflunine. Pembrolizumab significantly prolonged median OS in the overall population (10.3 *vs.* 7.4 months; P=0.002). Furthermore, lower incidence of treatment-related adverse events was reported in the experimental group. Therefore, pembrolizumab is an approved treatment option in the second-line setting. Similar results were obtained by atezolizumab in UC post-platinum treatment. Following the encouraging results obtained in the phase II IMvigor210 trial cohort 2 (18), the results obtained in the randomised phase III IMvigor211 study (33,34), however, did not exhibit statistically significant longer median OS in comparison with standard second-line chemotherapy. Therefore, Genentech/Roche voluntarily withdrew the U.S. indication of second-line atezolizumab in advanced UC (35). Nivolumab, durvalumab and avelumab were also studied in phase I/II studies enrolling advanced UC patients progressing after first-line platinum-based chemotherapy and showed efficacy and safety comparable to the data obtained in different trials by atezolizumab and pembrolizumab, with median OS of around 8–10 months and ORR 10–25%. In these trials, PD-L1 expression level was not associated with significantly higher efficacy of ICIs, and therefore patient selection according to PD-L1 status is not routinely advised when using these products in second-line treatment for advanced UC (23,36-39) (*Table 1*). More recently, the anti-PD-1 monoclonal antibody tislelizumab was engineered to minimize linking to the Fc gamma receptor on macrophages in order to mitigate antibody-dependent phagocytosis, a postulated mechanism of T-cell clearance and treatment resistance. Tislelizumab was studied in Asian UC patients previously treated with platinum-containing chemotherapy. The ORR observed was 24%, with median PFS and OS times of 2.1 and 9.8 months, respectively (40). These results led to the approval of tislelizumab by the China National Medical Products Administration (NMPA) as a second-line

Table 1 Second-line immune checkpoint inhibitors for metastatic UC. Results from most representative trials

Trial name	Trial phase	Experimental arm	Efficacy outcomes
Keynote-045	3	Pembrolizumab 200 mg IV every 3 weeks (n=266)	ORR 21.9%
			mPFS 2.1 months
			mOS 10.3 months
IMvigor211	3	Atezolizumab 1,200 mg IV every 3 weeks (n=467)	ORR 23%
			mPFS 2.1 months
			mOS 11.1 months
Checkmate 275	2	Nivolumab 240 mg IV every 2 weeks (n=270)	ORR 20.7%
			mPFS 1.9 months
			mOS 8.6 months
Study 1108	1/2	Durvalumab 10 mg/Kg IV every 2 weeks (n=191)	ORR 17.8%
			mPFS 1.5 months
JAVELIN Solid Tumour	1/2	Avelumab 10 mg/kg IV every 2 weeks (n=44)	ORR 16.5%
			mPFS 1.5 months
			mOS 7.0 months
NCT04004221	2	Tislelizumab 200 mg IV every 3 weeks (n=113)	ORR 24%
			mPFS 2.1 months
			mOS 9.8 months

IV, intravenous; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival.

treatment for advanced UC patients, and this drug may also enter the European Union (EU) market in the near future.

Innovative approaches and drugs under clinical development

The development of novel, effective treatment options remains an important area of unmet need, especially for patients who are cisplatin-ineligible. Apart from ICIs, enfortumab vedotin is one of the most promising drugs in the UC scenario. Enfortumab vedotin is an antibody drug conjugate directed against nectin-4, which is overexpressed in most UCs. Monomethyl auristatin E, an anti-microtubule agent, is the chemotherapeutic part linked to the monoclonal antibody. Enfortumab vedotin has shown to be quite active in advanced UC, showing remarkable anti-tumour activity in patients already exposed to platinum-based chemotherapy and ICIs (5). Preclinical data show that antibody drug conjugates may increase tumour immunogenicity by induction of immunogenic cell death, enhanced tumour antigen presentation, and tumour infiltration (41). Therefore, combining enfortumab vedotin with an ICI might improve the response rate and act synergistically in order to prolong PFS and OS in patients with advanced UC. The combination of enfortumab vedotin and pembrolizumab was tested in the EV-103 trial (42), showing a staggering response rate of 64.5% in the first-line setting. The EV-302 trial (43) is a two-arm, open-label, randomized controlled phase III study investigating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in previously untreated advanced UC. The trial results may pave the way for a new standard of care in the first-line setting. Sacituzumab govitecan is an emerging antibody drug conjugated targeting TROP-2, which is widely expressed in normal urothelium and most UCs. In the TROPHY-U-01 phase II trial, patients with advanced UC pre-treated with platinum-based chemo and ICI were included in cohort 1. Patients were treated with sacituzumab govitecan monotherapy and obtained sufficient anti-tumour activity (ORR of 27%) to be granted accelerated FDA approval (44). An encouraging 34% ORR was reported in cohort 3, enrolling patients progressed after

platinum-based regimens and investigating sacituzumab govitecan in combination with pembrolizumab (45). ICIs in combination with tyrosine kinase inhibitors is an attractive field of investigation in several tumour types including UC, particularly in the setting of cisplatin-ineligible patients (46). In the phase III LEAP-011 trial (47), however, the combination lenvatinib plus pembrolizumab recently failed to show superior anti-tumour activity when compared with placebo plus pembrolizumab as frontline therapy in advanced UC patients who were ineligible to cisplatinum. Additional combinations are still under investigation, including cabozantinib in combination with pembrolizumab or other ICIs (46). UC has been shown to express FGFRs. FGFRs are a family of receptor tyrosine kinases involved in tumour proliferation and cancer cell migration (48). FGFR3 is the most frequently hyperactivated of the FGFRs in UC, and its genetic alterations are found in around 20% of advanced UC. FGFR inhibitors target these receptors and show promise as a drug class. Erdafitinib, a pan-FGFR tyrosine kinase inhibitor, was shown to be clinically active and tolerable in patients with advanced UC and prespecified FGFR alterations in the BLC2001 study, leading to the regulatory approval of this drug (49). Literature evidence suggests that ICIs may have inferior response in UC harbouring FGFR alterations, possibly due to factors related to the tumour microenvironment (50-52). Several ongoing trials are still evaluating FGFR inhibitors in advanced UC, including the ongoing phase Ib/II NORSE trial combining erdafitinib plus the ICI cetrelimab in cisplatin-ineligible patients. Preliminary results presented at the European Society for Medical Oncology (ESMO) Congress 2022 showed promising anti-tumour activity for the combination (53). Cancer vaccines represent another way to activate the immune system, eliciting specific antibodies or cytotoxic immune responses directed against cancer cells. UC has quite a long and rewarding history of vaccines use, starting from the BCG, which still represents a milestone for the treatment of non-muscle invasive bladder cancer since its introduction more than 30 years ago (7). In advanced UC, preliminary studies have mainly tested cancer vaccines in the forms of dendritic cells and peptide vaccines, but these products have so far been unsuccessful in progressing to later phases of drug development due to the modest clinical activity observed (54). The combination of cancer vaccines with other regimens would warrant further investigation, as it could potentially maximize the benefit of this type of therapy. For instance, NeoPepVac (55) is an ongoing pivotal trial investigating the safety and activity of a personalised neo-antigen vaccine containing up to 15 peptides obtained from the individual patient's tumour. In this study the cancer vaccine is being combined with an anti-PD-1 or anti-PD-L1 agent in advanced solid tumours, including patients with UC. Tumour-infiltrating lymphocyte (TIL) therapy is one of the several treatment modalities known collectively as adoptive cell therapy, which involves harnessing the patient's own immune system to obtain anti-tumour activity. TILs are collected from the tumour during a biopsy or surgical resection, and then stimulated and expanded to very large numbers *in vitro* with interleukin-2 (IL-2). The patient undergoes lymphodepletion with a brief course of chemotherapy before the infusion of the laboratory-grown TILs. TIL therapy has already shown to have remarkable anti-cancer activity in haematological malignancies, melanoma, and cervical, lung and head and neck cancers (56-60). It is hoped that further progress in TIL therapies will improve response rates further and enable this innovative treatment modality to become an available option across a wider range of solid malignancies, including UC (61,62). Historically, high-dose IL-2 therapy has been able to confer sustained clinical benefit in selected patients with immunogenic cancers such renal cell carcinoma and melanoma, partly through lymphoid expansion. Nevertheless, it is associated with severe toxicity requiring in-patient administration at specialist centres, thereby limiting its use (63). Bempegaldesleukin is a CD122-preferential IL-2 pathway agonist that has shown capacity to induce proliferation and activation of T cells and NK cells in the circulation and tumour microenvironment, including increased expression of PD-1 on cancer cells, in patients with advanced solid tumours (64). In the recent phase II PIVOT-02 trial, bempegaldesleukin in combination with nivolumab showed good tolerability and promising anti-tumour activity as first-line treatment in patients with advanced UC (65), but subsequent disappointing efficacy results in the phase II PIVOT-10 study and other phase III trials in renal cell carcinoma and melanoma led to the discontinuation of the development program of bempegaldesleukin (66). Exploring the role of novel predictive factors of response to ICIs is another important research strategy in advanced UC. Dostarlimab received FDA approval for the treatment of advanced gynaecological malignancies with mismatch repair deficiency or microsatellite instability (67). Lynch syndrome, commonly known as hereditary non-polyposis colorectal cancer, is an autosomal-dominant familial cancer

syndrome with an increased risk of UC. Indeed, there are limited reports suggesting that individuals with Lynch syndrome-related UC may receive significant benefit from ICIs (68). Baseline or early change in neutrophil-to-lymphocyte ratio has shown the potential to identify patients that may benefit the most from ICIs (29,69,70). Gut microbiome is emerging as a key factor in determining the balance between human health and disease (71). Growing literature evidence supports that microbiome heavily affects the therapeutic efficacy of cancer immunotherapy, particularly ICIs (72). Ongoing research is aiming at further exploring the field, and hopefully the manipulation of the gut microbiome may help enhancing the efficacy of immunotherapy in advanced UC and other malignancies in the future.

Conclusions

ICIs are revolutionising the systemic treatment of many malignant tumours, including advanced UC, providing durable responses with a favourable safety profile. Apart from PD-L1 expression, there remains an unmet need for successful implementation of valuable predictive factors that may optimise treatment selection. The immunomodulatory effect of the gut microbiome, for instance, is emerging as a critical factor and could potentially cover this unmet need. UC is undoubtedly chemosensitive, and platinum-based chemotherapy still retains a significant role in the management of advanced/metastatic disease. However, ICI combined with enfortumab vedotin and/or FGFR inhibitors may change the current scenario in the near future, whereas further research is warranted in order to implement novel immunotherapy modalities in the therapeutic armamentarium.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*, for the series "Medical Oncology: Challenges in 2022". The article has undergone external peer review.

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037apm-22-1350/prf.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1350/coif). The series "Medical Oncology: Challenges in 2022" was commissioned by the editorial office without any funding or sponsorship. MM is a full-time Novartis employee and Novartis shareholder. SB served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432-8.
2. Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:931-45.
3. Köberle B, Tomicic MT, Usanova S, et al. Cisplatin resistance: preclinical findings and clinical implications. Biochim Biophys Acta 2010;1806:172-82.
4. Oing C, Rink M, Oechsle K, et al. Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond-A Comprehensive Review of the Current Literature. J Urol 2016;195:254-63.
5. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021;384:1125-35.
6. Montazeri K, Bellmunt J. Erdafitinib for the treatment of metastatic bladder cancer. Expert Rev Clin Pharmacol

2020;13:1-6.
7. Alexandroff AB, Jackson AM, O'Donnell MA, et al. BCG immunotherapy of bladder cancer: 20 years on. Lancet 1999;353:1689-94.
8. Tesniere A, Panaretakis T, Kepp O, et al. Molecular characteristics of immunogenic cancer cell death. Cell Death Differ 2008;15:3-12.
9. Kraehenbuehl L, Weng CH, Eghbali S, et al. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. Nat Rev Clin Oncol 2022;19:37-50.
10. Tripathi A, Plimack ER. Immunotherapy for Urothelial Carcinoma: Current Evidence and Future Directions. Curr Urol Rep 2018;19:109.
11. Ali R, Rakha EA, Madhusudan S, et al. DNA damage repair in breast cancer and its therapeutic implications. Pathology 2017;49:156-65.
12. Boussios S, Rassy E, Moschetta M, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers (Basel) 2022;14:3888.
13. Addeo A, Friedlaender A, Banna GL, et al. TMB or not TMB as a biomarker: That is the question. Crit Rev Oncol Hematol 2021;163:103374.
14. Powles T, Walker J, Andrew Williams J, et al. The evolving role of PD-L1 testing in patients with metastatic urothelial carcinoma. Cancer Treat Rev 2020;82:101925.
15. Hansen AR, Siu LL. PD-L1 Testing in Cancer: Challenges in Companion Diagnostic Development. JAMA Oncol 2016;2:15-6.
16. Burgess EF, Livasy C, Hartman A, et al. Discordance of high PD-L1 expression in primary and metastatic urothelial carcinoma lesions. Urol Oncol 2019;37:299.e19-25.
17. Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol 2017;18:1600-9.
18. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:1483-92.
19. Vuky J, Balar AV, Castellano D, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. J Clin Oncol 2020;38:2658-66.
20. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67-76.
21. Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1547-57.
22. Galsky MD, Arranz JÁ, Grande E, et al. Atezolizumab (atezo) + platinum/gemcitabine (plt/gem) vs placebo + plt/gem in patients (pts) with previously untreated locally advanced or metastatic urothelial carcinoma (mUC): Updated overall survival (OS) from the randomized phase III study IMvigor130. Cancer Res 2021;81:abstr CT042.
23. Flaig TW, Spiess PE, Abern M, et al. NCCN Guidelines® Insights: Bladder Cancer, Version 2.2022. J Natl Compr Canc Netw 2022;20:866-78.
24. Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:244-58.
25. Lopez-Beltran A, Cimadamore A, Blanca A, et al. Immune Checkpoint Inhibitors for the Treatment of Bladder Cancer. Cancers (Basel) 2021;13:131.
26. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020;21:1574-88.
27. Available online: https://www.medthority.com/news/2022/5/update-on-checkmate--901-trial-evaluating-opdivo--yervoy-as-first-line-treatment-for-unresectable-or-metastatic-urothelial-carcinoma-bladder-cancer.--bms/
28. Geynisman DM, Broughton E, Hao Y, et al. Real-world treatment patterns and clinical outcomes among patients with advanced urothelial carcinoma in the United States. Urol Oncol 2022;40:195.e1-195.e11.
29. Yip SM, Kaiser J, Li H, et al. Real-world Outcomes in Advanced Urothelial Cancer and the Role of Neutrophil to Lymphocyte Ratio. Clin Genitourin Cancer 2018;16:e637-44.
30. Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2020;383:1218-30.
31. Duan J, Cui L, Zhao X, et al. Use of Immunotherapy With Programmed Cell Death 1 vs Programmed Cell Death

Ligand 1 Inhibitors in Patients With Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2020;6:375-84.
32. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.
33. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748-57.
34. van der Heijden MS, Loriot Y, Durán I, et al. Atezolizumab Versus Chemotherapy in Patients with Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: A Long-term Overall Survival and Safety Update from the Phase 3 IMvigor211 Clinical Trial. Eur Urol 2021;80:7-11.
35. Rhea LP, Aragon-Ching JB. Advances and Controversies With Checkpoint Inhibitors in Bladder Cancer. Clin Med Insights Oncol 2021;15:11795549211044963.
36. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-22.
37. Galsky MD, Saci A, Szabo PM, et al. Nivolumab in Patients with Advanced Platinum-resistant Urothelial Carcinoma: Efficacy, Safety, and Biomarker Analyses with Extended Follow-up from CheckMate 275. Clin Cancer Res 2020;26:5120-8.
38. Powles T, O'Donnell PH, Massard C, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. JAMA Oncol 2017;3:e172411.
39. Apolo AB, Ellerton JA, Infante JR, et al. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN Solid Tumor study: 2-year updated efficacy and safety analysis. J Immunother Cancer 2020;8:e001246.
40. Ye D, Liu J, Zhou A, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer Sci 2021;112:305-13.
41. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. Nat Rev Clin Oncol 2021;18:327-44.
42. Rosenberg JE, Milowsky M, Ramamurthy C, et al. LBA73 - Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC). Ann Oncol 2022;33:S808-69.
43. van der Heijden MS, Gupta S, Galsky MD, et al. 798TiP - Study EV-302: A 3-arm, open-label, randomized phase III study of enfortumab vedotin plus pembrolizumab and/or chemotherapy, versus chemotherapy alone, in untreated locally advanced or metastatic urothelial cancer. Ann Oncol 2020;31:S550.
44. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol 2021;39:2474-85.
45. Grivas P, Pouessel D, Park CH, et al. TROPHY-U-01 Cohort 3: Sacituzumab govitecan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens. J Clin Oncol 2022;40:abstr 434.
46. Brown JR, Krane S, Garcia J, et al. Outlook into the future of front-line immune checkpoint inhibition in metastatic urothelial carcinoma. Ther Adv Urol 2021;13:17562872211004797.
47. Loriot Y, Grivas P, De Wit R, et al. First-line pembrolizumab (pembro) with or without lenvatinib (lenva) in patients with advanced urothelial carcinoma (LEAP-011): A phase 3, randomized, double-blind study. J Clin Oncol 2022;40:abstr 432.
48. Szybowska P, Kostas M, Wesche J, et al. Cancer Mutations in FGFR2 Prevent a Negative Feedback Loop Mediated by the ERK1/2 Pathway. Cells 2019;8:518.
49. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2019;381:338-48.
50. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-20.
51. Santiago-Walker AE, Chen F, Loriot Y, et al. Predictive value of fibroblast growth factor receptor (FGFR) mutations and gene fusions on anti-PD-(L)1 treatment outcomes in patients (pts) with advanced urothelial cancer (UC). J Clin Oncol 2019;37:abstr 419.
52. Rezazadeh A, Loriot Y, Papantoniou D, et al. 757P An observational study of outcomes of patients (pts) with advanced urothelial carcinoma (UC) after antiprogrammed death-(ligand) 1 (PD-[L]1) therapy by fibroblast growth

factor receptor gene alteration (FGFRa) status. Ann Oncol 2020;31:S586-7.
53. Siefker-Radtke AO, Loriot Y, Siena S, et al. 752P Updated data from the NORSE trial of erdafitinib (ERDA) plus cetrelimab (CET) in patients (pts) with metastatic or locally advanced urothelial carcinoma (mUC) and specific fibroblast growth factor receptor (FGFR) alterations. Ann Oncol 2022;31:S584-5.
54. Maiorano BA, Schinzari G, Ciardiello D, et al. Cancer Vaccines for Genitourinary Tumors: Recent Progresses and Future Possibilities. Vaccines (Basel) 2021;9:623.
55. Available online: https://clinicaltrials.gov/ct2/show/NCT03715985
56. Ok CY, Young KH. Checkpoint inhibitors in hematological malignancies. J Hematol Oncol 2017;10:103.
57. Revythis A, Shah S, Kutka M, et al. Unraveling the Wide Spectrum of Melanoma Biomarkers. Diagnostics (Basel) 2021;11:1341.
58. Tang Y, Zhang AXJ, Chen G, et al. Prognostic and therapeutic TILs of cervical cancer-Current advances and future perspectives. Mol Ther Oncolytics 2021;22:410-30.
59. Hashemi S, Fransen MF, Niemeijer A, et al. Surprising impact of stromal TIL's on immunotherapy efficacy in a real-world lung cancer study. Lung Cancer 2021;153:81-9.
60. Almangush A, De Keukeleire S, Rottey S, et al. Tumor-Infiltrating Lymphocytes in Head and Neck Cancer: Ready for Prime Time? Cancers (Basel) 2022;14:1558.
61. Hinrichs CS, Rosenberg SA. Exploiting the curative potential of adoptive T-cell therapy for cancer. Immunol Rev 2014;257:56-71.
62. Zhao Y, Deng J, Rao S, et al. Tumor Infiltrating Lymphocyte (TIL) Therapy for Solid Tumor Treatment: Progressions and Challenges. Cancers (Basel) 2022;14:4160.
63. McDermott DF, Cheng SC, Signoretti S, et al. The high-dose aldesleukin "select" trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res 2015;21:561-8.
64. Bentebibel SE, Hurwitz ME, Bernatchez C, et al. A First-in-Human Study and Biomarker Analysis of NKTR-214, a Novel IL2Rβγ-Biased Cytokine, in Patients with Advanced or Metastatic Solid Tumors. Cancer Discov 2019;9:711-21.
65. Tannir NM, Cho DC, Diab A, et al. Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: results from the PIVOT-02 study. J Immunother Cancer 2022;10:e004419.
66. Nektar and Bristol Myers Squibb announce update on clinical development program for bempegaldesleukin (BEMPEG) in combination with Opdivo (nivolumab). News release. Nektar Therapeutics and Bristol Myers Squibb. April 14, 2022. Available online: https://bit.ly/3jUoSII
67. Singh V, Sheikh A, Abourehab MAS, et al. Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. Biosensors (Basel) 2022;12:617.
68. Lindner AK, Schachtner G, Tulchiner G, et al. Lynch Syndrome: Its Impact on Urothelial Carcinoma. Int J Mol Sci 2021;22:531.
69. Moschetta M, Uccello M, Kasenda B, et al. Dynamics of Neutrophils-to-Lymphocyte Ratio Predict Outcomes of PD-1/PD-L1 Blockade. Biomed Res Int 2017;2017:1506824.
70. Banna GL, Di Quattro R, Malatino L, et al. Neutrophil-to-lymphocyte ratio and lactate dehydrogenase as biomarkers for urothelial cancer treated with immunotherapy. Clin Transl Oncol 2020;22:2130-5.
71. Uccello M, Malaguarnera G, Basile F, et al. Potential role of probiotics on colorectal cancer prevention. BMC Surg 2012;12 Suppl 1:S35.
72. Lee KA, Shaw HM, Bataille V, et al. Role of the gut microbiome for cancer patients receiving immunotherapy: Dietary and treatment implications. Eur J Cancer 2020;138:149-55.

Cite this article as: Uccello M, Adeleke S, Moschetta M, Ghose A, Boussios S. Immunotherapy for advanced urothelial carcinoma (UC): rational and current evidence. Ann Palliat Med 2023. doi: 10.21037/apm-22-1350