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Recent therapeutic advances in urothelial carcinoma: A paradigm shift in disease management

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ABSTRACT

Management of first-line advanced urothelial carcinoma (UC) has consisted during the past three decades in the administration of platinum-based chemotherapy followed by observation. Despite moderate to high response rates to first-line treatment, most patients will relapse shortly after and the outcomes with subsequent therapies are poor with 5-year overall survival rates of 5% in the pre-immunotherapy era. Nonetheless, recent therapeutic developments including the paradigm shift of first-line maintenance therapy with avelumab after response or stabilization on platinum-based chemotherapy, along with the incorporation of new drug classes in further lines of treatment such as antibody drug-conjugates and fibroblast growth factor receptor inhibitors have reshaped the field leading to better outcomes in this patient population. This article reviews the current state of the art with an overview on UC management, recent advances, and the upcoming strategies currently in development in advanced UC with an insight into the biology of this disease.

1. Introduction

Bladder cancer is the tenth most common form of cancer globally, with 573,278 new cases and 212,536 related deaths estimated in 2020 (World Health Organization, 2020). Bladder cancer is almost four times more common in men than in women, being the sixth most common tumor and the ninth leading cause of cancer death in men (Bray et al., 2018). The median age at diagnosis is 73 years, with cigarette smoking increasing the risk of bladder cancer four-fold in western society (Saginala et al., 2020).

The most frequent histology of bladder cancer is urothelial carcinoma (UC). UC can occur anywhere along the urinary tract. More than 90% of UCs originate in the bladder, while the remaining originate in the renal pelvis, ureters, and urethra (National Cancer Institute, 2022). Less common types of bladder cancer named "variant histological types" are squamous cell carcinoma (3%), adenocarcinoma (2%), and small cell carcinoma (<1%), among others. Mixed histology is often seen, consisting predominantly of UC with areas of other types of variant histologies (Humphrey et al., 2016).

UCs are classified into three categories depending on the invasion of the bladder wall and the presence of metastasis: non-muscle invasive bladder cancer (NMIBC), that is limited to the urothelium not beyond the lamina propria; muscle invasive bladder cancer (MIBC), that grows in the lamina propria and invades the muscle layer; and unresectable

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locally advanced or metastatic UC (mUC), when it has spread to regional lymph nodes, abdominal or pelvic wall or distant sites (Bochner et al., 2017).

At diagnosis, around two thirds of patients present with NMIBC, of whom 10–15% will progress to invasive forms, being mainly high-risk cases. About 30% of the patients are diagnosed with MIBC and 10–15% present initially with locally advanced or metastatic disease. Additionally, around 50% of MIBC patients will relapse after radical cystectomy and develop metastasis (National Cancer Institute, 2022; Bajorin, 2016; Bellmunt et al., 2014; Milowsky et al., 2016).

Overall survival (OS) at 5 years considering all bladder cancer stages is approximately 77% in the US. However, OS is especially poor in the majority of patients with mUC (4.6% at 5 years in the pre-immunotherapy era) (Saginala et al., 2020).

The goal of treatment in NMIBC is to prevent recurrence and/or progression to invasive forms. Patients receive complete transurethral resection of the bladder tumor (TURBT). Subsequent treatment could include intravesical instillation with mitomycin C or Bacillus Calmette-Guérin (BCG) according to the risk group (Bajorin, 2016; Bellmunt et al., 2014; National Cancer Institute, 2022). Treatment of NMIBC remained unchanged until the introduction of checkpoint inhibitors (CPIs). In a phase II single arm trial (KEYNOTE-057), pembrolizumab in 103 patients with BCG-unresponsive carcinoma in situ (CIS) who were ineligible for or declined radical cystectomy showed a complete response (CR) rate at 3 months of 41%, with a median duration of CR of 16.2 months. Forty-six percent of initial responders had a CR that lasted at least 12 months (Balar et al., 2021). Based on this trial, pembrolizumab was granted US Food and Drug Administration (FDA) approval in January 2020 for patients with BCG-unresponsive high-grade NMIBC - CIS with or without papillary tumors (Food and Drug Administration, 2022a). Several trials are underway to evaluate the role of CPIs in the treatment of naïve NMIBC either alone or combined with BCG (POTOMAC trial, NCT03528694; CREST trial, NCT04165317; ALBAN trial, NCT03799835; and KEYNOTE-676 trial, NCT03711032), or after BCG failure (CheckMate 7G8 trial, NCT04149574; KEYNOTE-676 trial, NCT03711032; CREST trial, NCT04165317; and ADAPT trial, NCT03317158). Intravesical gene therapy with nadofaragene firadenovec also shows efficacy in this therapeutically challenging disease state (N = 103; 53% CR at 3 months; 24% CR at 12 months) with not yet regulatory approval (Boorjian et al., 2021).

In the MIBC setting, the goal is to increase the potential for cure while minimizing morbidity (Bajorin, 2016). Although bladder preservation strategies through trimodality therapy combining complete TURBT, radiation, and concurrent chemotherapy (CT) are increasing, radical cystectomy and pelvic lymph node dissection are still the gold standard for the management of MIBC (Gakis et al., 2013; Witjes et al., 2021). If the patient is eligible for cisplatin treatment, neoadjuvant cisplatin-based combination CT should be given (Witjes et al., 2021; Advanced Bladder Cancer ABC Meta-analysis Collaboration, 2005). Adjuvant cisplatin CT is not considered as standard of care (SoC) in these patients, although it is recommended for patients with high-risk tumors who did not receive neoadjuvant CT (Witjes et al., 2021; Leow et al., 2014).

The use of CPIs may also change the SoC in the near future for MIBC disease. While promising results have been reported for single arm phase II trials (NABUCCO, PURE-01, ABACUS, MDACC, NCT, and others), some neo-adjuvant phase III clinical trials are underway looking to confirm the benefit in this setting (NIAGARA, NCT03732677; CA017–078, NCT03661320; KEYNOTE-866, NCT03924856; KEYNOTE-B15/EV-304, NCT04700124; CA045–009, NCT04209114) (Rouanne et al., 2020). Additionally, several phase II trials are currently testing the combination of CPIs with CT in the neoadjuvant setting and some of them have already reported preliminary results (Rose et al., 2021; Martinez Chanza et al., 2021; Gupta et al., 2020; Funt et al., 2021).

Three randomized phase III trials have investigated the role of CPIs (atezolizumab, nivolumab, and pembrolizumab) in the adjuvant setting for MIBC who are at high risk of recurrence following resection. Whereas IMvigor-010 trial did not meet its primary endpoint of disease-free survival (DFS) for atezolizumab compared to observation (Bellmunt et al., 2021), CheckMate 274 has recently demonstrated that adjuvant nivolumab is associated with both statistically significant and clinically meaningful improvement in DFS compared to placebo in patients with MIBC following radical surgery, both in the intention-to-treat (ITT) population and in patients with programmed death-ligand 1 (PD-L1) $\geq$ 1%. OS data is still immature (Bajorin et al., 2021). Adjuvant nivolumab has received recent FDA approval in August 2021. Observation versus placebo used differently in the control arms of these two studies might potentially explain the differences observed on trial outcome. Results from the Ambassador study with pembrolizumab in this setting are still pending at the time of writing this review (NCT03244384). Furthermore, based on a retrospective biomarker analysis performed on the IMvigor010, another phase III trial with atezolizumab as adjuvant therapy is now accruing in select patients with high-risk MIBC who are positive for circulating tumor DNA (ctDNA+) post cystectomy (IMvigor011; NCT02302807).

Treatment in the unresectable locally advanced or metastatic setting is mainly palliative. For the past almost 30 years, cisplatin-based CT followed by observation was the SoC for patients who could tolerate cisplatin. In patients ineligible for cisplatin, carboplatin-based CT followed by observation was recommended (Bellmunt et al., 2014).

First-line platinum-containing CT in metastatic treatment-naïve patients result in objective response rates (ORR) in the range of 40–60% and disease control rates of nearly 80% of patients, however, progression-free survival (PFS) and OS are short because of primary or acquired CT resistance (von der Maase et al., 2000; Dogliotti et al., 2007; de Santis et al., 2012; von der Maase et al., 2005). Real-world studies have shown that in the pre-immunotherapy era, a considerable proportion of mUC patients were not receiving any systemic therapy at the time of progression, with only 25–55% of patients receiving second-line. In addition, outcomes with second-line therapy remain suboptimal because of rapid disease progression (Cheeseman et al., 2020; Aly et al., 2019; Galsky et al., 2018; Fisher et al., 2018; Niegisch et al., 2018; Flannery et al., 2019; Swami et al., 2021).

CPIs have shown antitumor activity against locally advanced and mUC and have shaped the management of the disease (Lopez-Beltran et al., 2021). These drugs were initially assessed as salvage treatment following progression on platinum-containing CT and showed favorable efficacy and safety profiles compared with cytotoxic CT (Plimack et al., 2017; Sharma et al., 2017; Rosenberg et al., 2016; Patel et al., 2018; Massard et al., 2016). Consequently, five PD-L1/PD-1 inhibitors (atezolizumab, nivolumab, pembrolizumab, avelumab, and durvalumab) received FDA approval and three PD-L1/PD-1 inhibitors (atezolizumab, nivolumab, and pembrolizumab) received European Medicines Agency (EMA) approval for the treatment of advanced UC in this setting.

With the aim of bringing forward the use of CPIs to the upfront setting, numerous therapeutic approaches have been developed, including the use of single agent CPI, the upfront combination of CT and CPIs, and the switch to a CPI as maintenance after non-progression to first-line CT. In PD-L1-positive patients ineligible for cisplatin, pembrolizumab or atezolizumab were a treatment option based on the results of phase II studies (Galsky et al., 2020; Powles et al., 2020; Powles et al., 2021; Powles et al., 2020). However, recently, FDA has restricted the use of pembrolizumab only to platinum ineligible patients irrespective of PD-L1 expression.

The objective of this article is to review latest advances and the paradigm shift in advanced UC treatment, including the role of immunotherapy and the recent approval of avelumab (anti-PD-L1) as first-line maintenance treatment of locally advanced or metastatic UC that has not progressed with first-line platinum-containing CT, the approval of two antibody drug-conjugate (ADC), enfortumab vedotin (EV) and sacituzumab govitecan (SG), after progression on platinum-based CT and CPIs, and of erdafitinib in patients with fibroblast growth factor (*FGFR*)

mutations or gene fusions in second or subsequent lines.

2. Therapeutic approach for locally advanced or metastatic disease

2.1. State of the art of first-line treatment

The standard first-line treatment for advanced or mUC is a platinum-containing combination (NCCN Guidelines®, 2021; Powles et al., 2021). Combinations of gemcitabine and cisplatin (GC) and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) plus granulocyte colony-stimulating factor regimens are accepted options in patients fit for cisplatin. The triplet combination of paclitaxel, gemcitabine and cisplatin (PGC) is another option for patients with mUC (Bellmunt et al., 2012). In the EORTC-30987 study, an increase in the ORR, a trend towards an improvement in PFS and a trend towards longer OS (3 months difference) was observed. Interestingly, PGC was associated with a significant improvement in OS among patients with primary bladder cancer compared with GC (median OS: 15.8 versus 12.7 months; HR 0.85; 95% CI 0.72–1.02; p = 0.075). An increase in febrile neutropenia with a lower incidence of thrombocytopenia and bleeding were observed in the PCG arm. These results suggest that PGC may be a treatment option for patients with mUC and indicate that it should be used for those with the bladder as primary origin. First-line GC and ddMVAC provide a median PFS of 7.7 and 9.5 months respectively, a median OS of 14.0 and 15.1 months and an ORR of 49.4% and 64% respectively (von der Maase et al., 2000; von der Maase et al., 2005; Sternberg et al., 2006). PCG provides a median PFS of 8.3 months, a median OS of 15.8 months and an ORR of 56%.

Around half of patients are ineligible or unfit for cisplatin according to the "Galsky criteria" (Galsky et al., 2011), because of impaired renal function (creatinine clearance < 60 ml/min), Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, peripheral neuropathy grade ≥ 2, New York Heart Association (NYHA) Class III heart failure, and/or hearing loss grade ≥ 2. In these patients considered unfit, carboplatin and gemcitabine (CbG) combination is a recommended option with lower activity than what is observed with cisplatin combinations (41% ORR and a median PFS and OS of 6 months and 9 months, respectively) (de Santis et al., 2012). Normally, four to six cycles of either cisplatin or carboplatin-based CT are given and then treatment is discontinued due to the lack of evidence of further treatment benefit and concerns about cumulative toxicity impairing patients' quality of life (von der Maase et al., 2000).

The limited long-term benefit obtained with CT led to a search for new strategies to prolong OS in first-line cisplatin-eligible and cisplatin-ineligible patients. CPIs have antitumor activity against UC in first-line cisplatin-ineligible patients and as salvage treatment in platinum-refractory patients. Switching to maintenance therapy with avelumab plus best supportive care (BSC) following non-disease progression with platinum-containing CT has demonstrated a statistically significant improvement in OS over BSC alone and is recommended as the new SoC in advanced and mUC patients with CR, partial response (PR) or SD to first-line platinum-containing CT by treatment guidelines in UC (NCCN Guidelines®, 2021; Powles et al., 2021; Cathomas et al., 2022). Combinations of CPI plus platinum-based CT or CPI plus CPI have not shown an OS benefit so far and additional studies are underway, which will be discussed later in this review (Galsky et al., 2020; Powles et al., 2020; Powles et al., 2021).

2.1.1. Checkpoint inhibitor monotherapy in first-line cisplatin-ineligible patients

Pembrolizumab and atezolizumab single agents were approved in 2017 and 2018 by the FDA and the EMA, respectively, in first-line for cisplatin-ineligible patients whose tumors express PD-L1. Additionally, and only in the United States, approval was granted for patients who were not eligible for any platinum-containing CT regardless of PD-L1 expression status (Food and Drug Administration, 2022b; European Medicines Agency, 2022). Accelerated approvals were initially based on the single-arm phase II KEYNOTE-052 study (Balar et al., 2017; Vuky et al., 2020; O'Donnell et al., 2021) and the IMvigor210 (Balar et al., 2017; Balar et al., 2018; Rosenberg et al., 2021) trials and are contingent upon confirmation from the first-line phase III studies KEYNOTE-361 (Powles et al., 2021) and IMvigor130 (Galsky et al., 2020). More recently, FDA has granted full approval and updated the indication of pembrolizumab restricting its use in first-line for the treatment of patients who are not eligible for any platinum-containing CT (Food and Drug Administration, 2021).

In KEYNOTE-052, pembrolizumab long-term results after 5 years of follow-up demonstrated an ORR of 28.9% with 9.5% of CRs, with a median duration of response (DOR) of 33.4 months. The median OS was 11.3 months, with a 24- and 36-month OS rate of 35.3% and 22.1%, respectively. Patients with a combined positive score (CPS) ≥ 10% had better outcomes than patients with CPS < 10%; (ORR 47.3% vs. 20.7%, and OS 18.5 months vs. 9.7 months, respectively) (O'Donnell et al., 2021).

In IMvigor210, atezolizumab long-term results after a minimum follow up of 5.8 years showed an ORR of 28% with a 12% CR. The ORR was 28% in patients with PD-L1 ≥ 5% in tumor-infiltrating immune cells (IC 2/3) and 22% in patients with PD-L1 < 1% (IC0/1). Median OS was 16.3 months, with a 2-year OS rate of 41%. Median DOR was 59.1 months in the all-comer population and 53.5 months in patients with PD-L1 IC0/1 tumors (IC2/3 median DOR not yet reached) (Rosenberg et al., 2021).

Preliminary analyses of the monotherapy arms from the phase III trials KEYNOTE-361 (pembrolizumab) and IMvigor130 (atezolizumab) assessing upfront CPI monotherapy versus platinum-based CT alone in advanced UC, identified a lower OS rate among patients with low PD-L1 expression treated with a CPI alone than among those who received platinum-based CT (Galsky et al., 2020; Powles et al., 2021). Based on these data, in 2016–2017 both the EMA and the FDA restricted the use of pembrolizumab and atezolizumab to patients with high expression of PD-L1 (Food and Drug Administration, 2022b), based on a predefined score and specific antibody against PD-L1 biomarker (22C3 or SP142). Due to the hierarchical design of both studies, the monotherapy arms were not formally tested, and results of these trials suggest that neither pembrolizumab nor atezolizumab monotherapy improved OS (Galsky et al., 2020; Powles et al., 2021).

A recent exploratory analysis from the IMvigor130 trial assessing efficacy outcomes for the atezolizumab monotherapy arm in cisplatin-ineligible patients based on PD-L1 status showed a median OS of 18.6 months for atezolizumab monotherapy (n = 50) versus 10 months for the CT arm (n = 43) (HR 0.53; 95% confidence interval [CI] 0.30–0.94) in PD-L1 positive (IC2/3) patients. Despite the exploratory nature of this analysis, it suggested an improved OS with atezolizumab monotherapy versus CT in cisplatin-ineligible PD-L1-positive patients (Galsky et al., 2021).

However, this trend was not observed in a similar exploratory analysis from KEYNOTE-361 assessing efficacy outcomes for pembrolizumab monotherapy versus CT in cisplatin-ineligible patients, which showed a median OS of 15.6 months for the pembrolizumab arm (n = 84) and 13.5 months for the CT arm (n = 89) (HR 0.82; 95% CI 0.57–1.17) in PD-L1 CPS ≥ 10% patients. Unlike IMvigor130, this analysis suggested that the PD-L1 CPS biomarker for pembrolizumab did not predict outcome with pembrolizumab in cisplatin-ineligible patients (Powles et al., 2021) and these results led the FDA to restrict pembrolizumab to platinum-ineligible patients (Food and Drug Administration, 2021).

Another recent phase III trial, the DANUBE study, also failed to show a statistically significant improvement for durvalumab monotherapy versus CT in the upfront setting of patients with high expression of PD-L1 (14.4 months versus 12.1 months, HR 0.89; 95% CI 0.71–1.11), although a survival benefit was observed with the combination of

durvalumab and tremelimumab in PD-L1-positive patients (secondary study endpoint) (Powles et al., 2020).

2.1.2. First-line maintenance approach

2.1.2.1. The rationale for maintenance therapy. Despite the activity seen with first-line platinum-based CT combinations, most patients with advanced UC will experience disease progression soon after concluding first-line treatment. Therefore, strategies to extend or improve the initial benefit achieved with platinum-based CT are required.

A possible solution could be the use of maintenance strategies, defined as a continuous treatment with a well-tolerated drug or combination of drugs after completing first-line induction therapy. Two maintenance approaches can be generally considered for patients who achieved an initial benefit with first-line treatment: i) a switch maintenance that means consecutive treatment with a different agent not used before; and ii) a continuation maintenance or deintensification that refers to the prolongation of one of the agents previously received as part of the induction treatment (Lee and Chung, 2014).

When designing a maintenance strategy, few points need to be considered. It is critical to carefully select as an induction treatment an agent or combination of agents capable of inducing a relevant degree of cytoreduction and somehow "priming" the tumor and its microenvironment to facilitate the action of a subsequent drug. More importantly, the subsequent regimen should not only be active by extending or increasing previously obtained responses but also should have a favorable safety profile, allowing long-term administration without impairment of patients' quality of life with ideally, an easy administration schedule. Additionally, the timing use of the sequentially utilized agent is critical. It has been hypothesized that a CT-free interval could decrease tumor resistance by removing a selective pressure, thereby allowing the re-expression of drug targets and the reversal of genetic and epigenetic changes, consequently leading to a less heterogeneous tumor and conditioning new sensitivity to the CT (Tonini et al., 2013).

Given these premises and the current treatment scenario in mUC, an attractive strategy seems to be a sequential approach of CT (a highly active induction strategy) followed, in those patients who achieved benefit, by immunotherapy maintenance (active and with low toxicity, allowing for long-term administration). Furthermore, there is a biological rationale for the sequential approach of these treatment options. On the one hand, CT is known to overcome tumor resistance by different mechanisms such as induction of immunogenic cell death, depletion of immunosuppressive cell types, increasing the presentation of tumor antigens, or triggering T-cell infiltration towards immunotherapy-resistant tumors. Recent data from IMvigor130 suggests that GC enhances anti-tumor immunity, particularly when is combined with atezolizumab, potentially through the induction of immunogenic cell death (Galsky et al., 2021). Therefore, administering CT first could modulate tumor resistance and eventually potentiate an immunotherapy effect (Emens and Middleton, 2015; Pfirschke et al., 2016). On the other hand, there could be a mechanistic explanation to justify this sequential approach using as a model, the cancer immunoediting framework, where elimination, equilibrium, and escape represent the different stages of the immune system-tumor interaction (Schreiber et al., 2011) (Fig. 1).

During the escape stage, when the tumor overcomes the immune system and proliferates, the anti-tumor effect of CT could help to restore the equilibrium phase or even lead to an elimination stage by decreasing

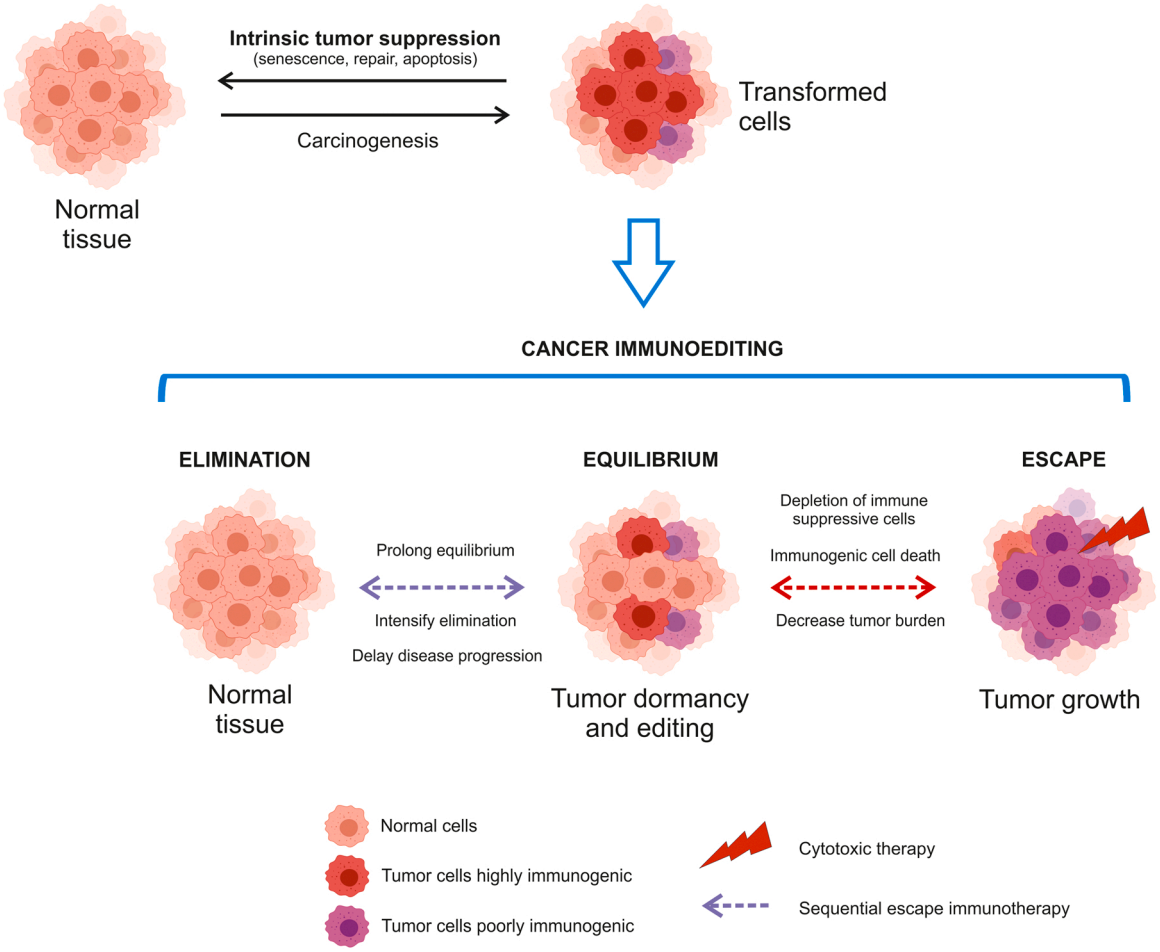

Fig. 1. Model of the cancer immunoediting framework.

or eliminating tumor burden. Nevertheless, these chemo-mediated effects may be transitory until tumor cells acquire immune escape mechanisms, and so the sequential administration of immunotherapy as a maintenance schedule may be crucial increasing the immune elimination and/or allowing the immune system to prolong the equilibrium phase, thereby delaying disease progression.

A switch-maintenance strategy may also enable more patients to receive a CPI within first-line therapy, rather than reserving it for the minority of patients who can receive it in second-line (Galsky et al., 2018; Flannery et al., 2019; Simeone et al., 2019). Previous attempts exploring the maintenance approach in mUC using sunitinib or lapatinib in genomically selected patients failed to show any benefit (Powles et al., 2017; Grivas et al., 2014). Vinflunine in the maintenance setting showed a PFS benefit without survival improvement (García-Donas et al., 2017; Bellmunt Molins et al., 2020).

2.1.2.2. First-line maintenance strategy with checkpoint inhibitors. Two randomized trials have been reported showing activity of switch maintenance therapy based on CPI upon non-progression from induction with platinum-based CT in the upfront setting of locally advanced or mUC: namely the Hoosier Cancer Research Network GU14–182 (HCRN GU14–182) trial and the JAVELIN Bladder 100 trial (Powles et al., 2020; Galsky et al., 2020). Comparative study design and main clinical outcomes of these two trials are shown in Table 1.

The first trial providing data with CPIs in the maintenance setting was the phase II randomized double-blinded investigator-initiated trial HCRN GU14–182, which compared pembrolizumab maintenance with placebo in 108 patients with advanced UC (Galsky et al., 2020). After receiving up to 8 cycles of platinum-based CT upfront, pembrolizumab showed a benefit in terms of PFS versus placebo (HR 0.65; $p = 0.04$). However, that difference was not translated into an improvement in OS (HR 0.91; 95% CI 0.52–1.59), probably due to the study design with small sample size and because of allowing placebo patients to crossover to pembrolizumab (51.9%) (Galsky et al., 2020).

Definitive evidence for the strategy of switch maintenance with CPI in advanced UC came from the phase III JAVELIN Bladder 100 trial (Powles et al., 2020). A total of 700 patients who did not have disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) criteria after an induction with 4–6 cycles of first-line platinum-based CT (GC or CbG) and a treatment-free interval (TFI) of 4–10 weeks from the last dose of CT, were randomized to receive avelumab at 10 mg/kg every 2 weeks plus BSC or BSC alone. Randomization was stratified according to the best response to first-line CT (CR or PR vs. SD) and to the metastatic site when first-line CT was initiated (visceral vs. non-visceral). Overall, 51% had PD-L1-positive tumors and 27% had upper urinary tract involvement. The primary endpoint was OS, assessed among the entire population and among those with PD-L1-positive tumors. Importantly, all the endpoints were measured post-randomization (after CT). At the prespecified interim analysis, the median follow-up was more than 19 months in each treatment arm. OS at 1 year was 71.3% in the avelumab group and 58.4% in the control group in the entire population. The median OS was 21.4 months and 14.3 months, respectively (HR 0.69; 95% CI 0.56–0.86). With a longer follow-up of more than 21 months in each arm, the benefit is maintained (median OS 22.1 vs. 14.6 months; HR 0.70; 95% CI 0.564–0.862) (European Medicines Agency, 2022). Clinical impact was also observed when medians of survival were compared (7.5 months of median OS increase) despite the fact that up to 43.7% of patients in the BSC group received subsequent treatment with an anti-PD-L1/PD-1 agent, favoring a maintenance approach versus second-line CPI treatment (Powles et al., 2020; European Medicines Agency, 2022). Avelumab significantly prolonged OS in the PD-L1-positive population too; OS at 1 year was 79.1% in the avelumab group and 60.4% in the control group (HR 0.56; 95% CI 0.40–0.79) (Powles et al., 2020; European Medicines Agency, 2022).

Avelumab maintenance treatment also improved PFS. The PFS rate at 12 months was 30% in the avelumab plus BSC versus 13% in the BSC arm (HR 0.62; 95% CI 0.52–0.75); the median PFS was 3.7 versus 2.0 months in the entire population. In the PD-L1-positive population, the PFS rate at 12 months was 36% in the avelumab plus BSC arm versus 15% in the BSC arm (HR 0.56; 95% CI 0.431–0.728); the median PFS was 5.7 versus 2.1 months, respectively (Powles et al., 2020).

The safety profile of avelumab during the maintenance period was consistent with the previously reported for avelumab monotherapy. Only 10.2% of infusion-related reactions were reported in the avelumab plus BSC arm and none of them were grade ≥ 3. The most frequent category of immune-related adverse events was thyroid disorders (12.2%) (Powles et al., 2020). Up to 11.9% of patients discontinued avelumab and 9.0% received high doses of steroids due to adverse events. The tolerability of avelumab plus BSC is supported by a no detrimental impact on clinically relevant patient-related outcomes compared to BSC alone, which is acceptable and reinforces the use of first-line avelumab maintenance as a new SOC for patients with advanced UC whose disease has no progressed with upfront platinum-containing CT (Powles et al., 2020). Treatment was given until progression.

Table 1
Trial design and main clinical outcomes of the maintenance strategy in advanced UC.

	Phase III JAVELIN Bladder 100 (Powles et al., 2020;European Medicines Agency, 2022)	Phase II HCRN GU14-182 (Galsky et al., 2020)
	N = 700	N = 108
Trial design	• Phase III • Open label • Avelumab plus BSC vs. BSC • Endpoints are measured post-randomization (after CT)	• Phase II • Double-blinded • Pembrolizumab vs. placebo • Endpoints are measured post-randomization (after CT)
Crossover	• No crossover to avelumab allowed	• Crossover to pembrolizumab allowed upon progression on placebo
Prior CT	• 4–6 cycles of induction platinum-based CT before randomization	• ≤ 8 cycles of induction CT before randomization
Dosing	• Avelumab Q2W	• Pembrolizumab Q3W
Primary endpoint	• OS	• PFS by Investigator
Tumor assessments	• Every 8 weeks	• Every 12 weeks
Countries / Sponsorship	• Global / Industry	• US / Investigator
Median PFS (ITT)	• PFS by IRC • Avelumab plus BSC: 3.7 months • BSC alone: 2.0 months (IC 95% 1.9–2.7) • Stratified HR 0.62 (95% CI 0.52–0.75); p < 0.001	• PFS by investigator • Pembrolizumab: 5.4 months • Placebo: 3.0 months • HR 0.65 (Log-rank p = 0.04)
Median OS (ITT)	• Avelumab plus BSC 22.1 months • BSC alone: 14.6 months Stratified HR 0.70 (95% CI 0.564, 0.862)	• Pembrolizumab: 22 months • Placebo: 18.7 months HR 0.91 (95% CI 0.52, 1.59)
Subsequent treatment with CPI (%)	43.7%	51.9%

Avelumab maintenance in first-line in patients with advanced or metastatic UC that have not progressed with platinum-based CT is the only treatment approved in this setting.
BSC: best supportive care; CI: confidence interval; CPI: checkpoint inhibitor; CT: chemotherapy; HCRN: Hoosier Cancer Research Network; HR: hazard ratio; IRC: Independent Review Committee; ITT: intention-to-treat; OS; overall survival; PFS: progression-free survival; NR: not reached; Q2W: once every 2 weeks; Q3W: once every 3 weeks.

Avelumab maintenance therapy showed a consistent trend towards improving survival in all subgroups of patients reported in the JAVELIN Bladder 100 trial (Powles et al., 2020). OS and PFS were longer with avelumab maintenance plus BSC versus BSC alone, both in patients who had received first-line GC and in those treated with a CbG. The former represented 52% and 59% in the experimental and control arm, respectively, and the latter 42% and 35% in each of the study arms. Moreover, the benefit for the maintenance arm with avelumab was independent of the type of response achieved with first-line CT (around 72% of patients in each arm showed a PR/CR after CT and 28% SD) (Powles et al., 2020). This was also irrespective of the duration or number of cycles of first-line CT received prior to randomization (Loriot et al., 2021) and of the length of the TFI from end of CT to the start of the maintenance treatment. In the TFI 4 to < 6 weeks subgroup, median OS was 19.9 vs. 13.5 months. In the TFI 6 to < 8 weeks subgroup, median OS was 26.1 vs. 21.0 months for avelumab + BSC and BSC alone, respectively (Sridhar et al., 2021). Subgroup analysis (as seen in the forest plot) might suggest that patients with PD-L1-negative status (OS HR 0.86; 95% CI 0.62–1.18; PFS HR 0.64; 95% CI 0.48–0.85) and patients who achieve CR with CT (25% in each arm) (OS HR 0.81; 95% CI 0.47–1.38; PFS HR 0.65; 95% CI 0.45–0.96) could have a reduced degree of benefit from avelumab than the overall population in terms of OS, although the PFS is significatively improved. Moreover, data in the CR group was not mature and PD-L1 was not an stratification factor, its value is discussed later on. Patients with visceral metastasis (HR 0.82; 95% CI 0.62–1.09; PFS HR 0.73; 95% CI 0.58–0.93), especially those with liver involvement (OS HR 0.92; 95% CI 0.54–1.56; PFS HR 0.96; 95% CI 0.59–1.55), might also benefit less from maintenance therapy, although this could reflect the worse prognosis associated with liver metastases and is only a hypothesis from the trial results (Grivas et al., 2020). Although the treatment sequence after progression to avelumab maintenance remains to be clarified, data for subsequent lines from JAVELIN Bladder 100 suggest that CT including platinum-based CT rechallenge and targeted therapies like erdafitinib are treatment options (Grivas et al., 2021).

Based on the JAVELIN Bladder 100 results, avelumab received FDA and EMA approvals in June 2020 and January 2021, respectively, for the maintenance treatment of patients with locally advanced or mUC who have not progressed with first-line platinum-containing CT and was added as a preferred or recommended treatment in the National Comprehensive Cancer Network (NCCN) (Category I) and European Society for Medical Oncology (ESMO) (category IA) guidelines, respectively (Powles et al., 2020; NCCN Guidelines®, 2021; Powles et al., 2021; Food and Drug Administration, 2022c; Inacio, 2022).

2.1.3. Other strategies in first-line

2.1.3.1. Checkpoint inhibitor plus chemotherapy as first-line combination approach. Two large phase III randomized studies evaluated this approach in first-line advanced or mUC: IMvigor130 and KEYNOTE-361 (Galsky et al., 2020; Powles et al., 2021). IMvigor130 was a three-arm trial that compared atezolizumab plus platinum-based CT and atezolizumab monotherapy versus placebo plus platinum-based CT (Galsky et al., 2020). The selection of GC or CbG in the CT regimen was based on investigator's choice. Co-primary efficacy endpoints were PFS and OS for atezolizumab plus CT versus CT, and following a hierarchical approach, OS for atezolizumab monotherapy versus CT was analyzed only if OS was positive for the combination arm versus CT. Patients were stratified according to PD-L1 immune cell expression status, Bajorin risk factor score, and investigator choice of platinum-based therapy (GC or CbG).

A total of 1213 patients were included. The final PFS analysis revealed a statistically significant difference in median PFS of 8.2 months for atezolizumab plus CT versus 6.3 months for CT (two months' increase in median PFS; HR 0.82; 95% CI 0.70–0.96) (Galsky et al., 2020). The second interim OS analysis with a median follow-up of 13.3 months did not cross the prespecified interim efficacy boundary for statistical significance (HR 0.84; 95% CI 0.71–1.00; one-sided p = 0.026) (Galsky et al., 2021). Longer follow-up is still required for final OS analysis. The combination of atezolizumab and CT was in general well tolerated, with a safety profile consistent with each individual agent (Galsky et al., 2020).

KEYNOTE-361 was an open-label three-arm trial that compared pembrolizumab plus platinum-based CT and pembrolizumab monotherapy versus CT alone (Powles et al., 2021). Randomization was stratified by investigator choice of platinum-based CT and the positivity for PD-L1 CPS. Co-primary endpoints were PFS and OS, using a hierarchical strategy: first, testing both PFS and OS for pembrolizumab plus CT versus CT alone; and followed by OS for pembrolizumab alone versus CT in CPS ≥ 10% and the entire population if the above analysis was positive.

The study included 1010 patients. With a median follow up of 31.7 months, differences in PFS and OS between pembrolizumab plus CT versus CT alone did not reach statistical significance according to the protocol prespecified criteria (one-sided p value boundary for significance of 0.0019 and 0.0033 for PFS and OS final analysis, respectively). Median PFS for pembrolizumab plus CT and CT alone was 8.3 and 7.1 months, respectively (HR 0.78; 95% CI 0.65–0.93). Median OS was 17.0 and 14.3 months, respectively (HR 0.86; 95% CI 0.72–1.02). DOR was 28.2 months versus 6.2 months with CT plus pembrolizumab and CT alone, respectively.

2.1.3.2. Two checkpoint inhibitors as first-line combination approach. The combination of two CPIs with different mechanisms of action and acting at different stages of immune activation is also an interesting approach (Harris et al., 2016). CTLA-4 is thought to regulate T-cell proliferation in the early stages of the immune response, primarily in lymph nodes, whereas PD-1 suppresses T-cells at later stages in peripheral tissues (Buchbinder and Desai, 2016).

The DANUBE study is a randomized phase III trial that compared durvalumab, an anti-PD-L1 agent, with or without tremelimumab, an anti-CTLA-4 agent, administered for up to a total of 4 doses, with standard CT (GC or CbG) up to a maximum of 6 cycles as first-line treatment for mUC (Powles et al., 2020). Randomization was stratified based on cisplatin eligibility, PD-L1 status (high vs. low expression) and presence/absence of liver and/or lung metastasis. The co-primary endpoints were OS of durvalumab versus CT for the population with high expression of PD-L1, and OS for durvalumab plus tremelimumab versus CT for the entire population.

A total of 1032 patients were included. The OS for durvalumab versus CT in the population with high expression of PD-L1 (tumor cells and/or immune cells [TC/IC ≥ 25]) was not significant (HR 0.89, 95% CI 0.71–1.11). The OS for durvalumab plus tremelimumab versus CT in the entire population was 15.1 months versus 12.1 months, respectively (HR 0.85; 95% CI 0.72–1.02). Evaluated as a secondary endpoint in the PD-L1-high expression population, the combination of durvalumab plus tremelimumab showed a statistically significant improvement for OS versus CT of 17.9 months versus 12.1 months, respectively (HR 0.74; 95% CI 0.59–0.93). Although in the entire population CT had the highest ORR (49%), in the PD-L1-high expression population (exploratory analysis) durvalumab plus tremelimumab arm had an ORR comparable to CT (47%). However, the median DOR was higher for the durvalumab and durvalumab plus tremelimumab versus CT arm (9.3 vs. 11.1 vs. 5.7 months in the entire population, and 18.5 vs. 10.0 vs. 5.8 months in the PD-L1-high expression population, respectively) (Powles et al., 2020). A recent exploratory analysis also suggests a role for the TC/IC ≥ 25 algorithm with the Ventana SP263 biomarker assay as a predictor of longer survival in patients treated with the combination of durvalumab plus tremelimumab or even durvalumab monotherapy (Bellmunt et al., 2021).

Furthermore, the results from the combination arm of nivolumab plus ipilimumab versus CT from the CheckMate 901 trial (Galsky et al., 2018) are still pending and will provide additional evidence on the role of the combination of two CPI in this setting.

2.1.3.3. Checkpoint inhibitor plus antibody-conjugated drug or targeted therapies as first-line combination approach. ADC therapies, such as EV, have shown promising results in second-line and further survival advantage in third-line treatment of mUC and are expected to move to upfront lines in combination with CPIs (Rosenberg et al., 2020; Powles et al., 2021; Rosenberg et al., 2019; Balar et al., 2021). EV is a Nectin-4 directed ADC comprised of a fully human anti-Nectin-4 IgG1 conjugated to the small molecule microtubule-disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimide caprol valine-citrulline linker (Chau et al., 2019; Food and Drug Administration, 2019). The antibody binds with high affinity to tumor cells expressing Nectin-4 that then internalizes and releases the chemotherapeutic agent, which arrests the cell cycle and induces apoptosis.

The phase I/II EV-103 study analyzed the combination of EV and pembrolizumab as first-line treatment in patients with advanced UC ineligible for cisplatin (Rosenberg et al., 2020; Friedlander et al., 2021). Five patients were included in the dose escalation phase, and 40 were included in the expansion cohort (Rosenberg et al., 2020). At a median follow-up of 24.9 months, confirmed ORR was 73.3%, including 17.8% CR. The median DOR was 25.6 months. The median PFS was 12.3 months, and the median OS was not reached, with an OS rate at 24 months of 56.3% (Friedlander et al., 2021). The most common treatment-related adverse events were peripheral sensory neuropathy (56%, 4% grade $\geq$ 3), fatigue (51%, 11% grade $\geq$ 3), and alopecia (49%) (Rosenberg et al., 2020).

Due to these results, the pivotal phase III EV-302 trial is underway. This trial originally compared EV plus pembrolizumab versus GC/CbG versus EV plus pembrolizumab and cisplatin or carboplatin as first-line treatment for advanced or mUC (NCT04223856). The enrollment of the third arm was discontinued in August 2020. The primary endpoints are PFS and OS.

Other ongoing studies include combinations of CPI with targeted therapies in randomized phase II trials like the NORSE trial (NCT03473743) of erdafitinib or erdafitinib plus cetrelimab for patients with *FGFR* alterations; the FORT-2 trial (NCT03473756) of rogaratinib in combination with atezolizumab in cisplatin-ineligible patients with *FGFR* alterations; or the FIGHT-205 trial (NCT04003610) of pemigatinib or pemigatinib plus pembrolizumab for cisplatin ineligible patients with *FGFR3* mutation or rearrangement, among others. The phase III trial LEAP-011 trial (NCT03898180) of lenvatinib and pembrolizumab combination in patients ineligible for platinum-based CT has been recently discontinued for futility (NCT03898180 Cg, 2022).

2.2. Comparing different novel first-line therapeutic approaches

Although the role of platinum-based CT remains a critical option in advanced UC, its administration partially depends on the presence or absence of medical comorbidities and the criteria for eligibility proposed by Galsky et al. (2011). It is well recognized that the use of cisplatin is associated with OS benefit and eligible patients not treated with cisplatin had a shorter median OS (Bamias et al., 2018). In addition, for patients who are ineligible for standard cisplatin-based CT, pembrolizumab and atezolizumab are alternative choices in EU for patients with high PD-L1 expression providing an alternative to carboplatin-based CT (Food and Drug Administration, 2022b; European Medicines Agency, 2022), although randomized trials have failed to show significant superiority compared with CT (Galsky et al., 2020; Powles et al., 2021).

Results from first-line chemo-immunotherapy trials in patients with mUC were recently published with disappointing results, suggesting that monotherapy with a CPI in first-line is not the optimal approach in the majority of patients (Galsky et al., 2020; Powles et al., 2021). The therapeutic strategy that seems to have provided the greatest robustness in terms of efficacy correspond to avelumab as first-line maintenance therapy in patients whose disease has not progressed with first-line platinum-based CT, based on the results of the JAVELIN Bladder 100 trial (Powles et al., 2020). Rapid introduction of post-platinum switch maintenance therapy with avelumab is the preferred option over treatment break since it delays disease progression and has shown a benefit in OS, with the longest OS ever achieved in a trial for patients with mUC. This strategy does not require PD-L1 testing for assessing eligibility for avelumab as the benefit is observed regardless PD-L1 status. Therefore, in line with the recent updated ESMO and NCCN guidelines, platinum-eligibility should guide therapeutic decisions in first-line advanced UC and platinum-based CT followed by maintenance avelumab is recommended and preferential compared with upfront CPI monotherapy in cisplatin-ineligible PD-L1 positive patients (Powles et al., 2020; NCCN Guidelines®, 2021; Powles et al., 2021; Food and Drug Administration, 2022c; Inacio, 2022). The recent FDA label change for pembrolizumab reinforces the idea that for cisplatin-ineligible PD-L1 positive patients, CbG followed by avelumab maintenance is the preferred option instead of pembrolizumab upfront. First-line treatment with CPI monotherapy could be limited to patients who are platinum-ineligible, have high PD-L1 expression and specific clinical characteristics (Table 2). Recent FDA label for pembrolizumab restricts its use to platinum ineligible without the need of testing for PD-L1 (Food and Drug Administration, 2021). Finally, ADCs targeting a highly expressed tumor protein and conjugated to a CT payload, such as for EV or SG, are emerging as effective therapies for subsequent lines of treatment. EV is being developed in a phase III in the upfront setting based on the promising results from the phase I/II EV-103 study of EV in combination with pembrolizumab (Rosenberg et al., 2020; Friedlander et al., 2021).

2.3. Second and later lines of treatment

A significant proportion of mUC patients do not receive second-line therapy due to deterioration or other comorbidities. For patients who receive second-line therapy, survival is progressively worse (Flannery et al., 2019; Simeone et al., 2019). Patients with mUC who have progressed on first-line treatment with platinum-based CT may choose to be treated with different drugs. Traditionally, they have been treated with CT based on vinflunine or taxanes (McCaffrey et al., 1997; Vaughn et al., 2002; Joly et al., 2009; Petrylak et al., 2017; Gómez de Liaño and Durán, 2018; de Santis et al., 2009; Sonpavde et al., 2016). Vinflunine showed an improvement in terms of survival compared to BSC in the eligible population analysis in a phase III study, while the efficacy of treatment with taxanes was derived from phase II studies (Gómez de Liaño and Durán, 2018; de Santis et al., 2009).

The good results obtained subsequently with anti-PD-L1/PD-1 drugs led to the approval of 5 different drugs: durvalumab, nivolumab, and avelumab (based on phase II studies) and atezolizumab and pembrolizumab (based on phase III comparative studies to standard CT) (Plimack et al., 2017; Sharma et al., 2017; Rosenberg et al., 2016; Massard et al., 2016; Sharma et al., 2016; Apolo et al., 2017; Bellmunt et al., 2017). The ORR obtained with the different drugs ranged between 13% and 24%, with a PFS between 1.5 and 2.8 months, and an OS between 7.7 and 10.3 months. The only phase III study that clearly demonstrated a statistically significant improvement in the OS was KEYNOTE-045, which randomly assigned 542 patients with advanced UC that recurred or progressed after platinum-based CT to receive pembrolizumab versus the investigator's choice of CT with paclitaxel, docetaxel, and vinflunine. With a median follow-up of 5 years, median OS was 10.1 months vs. 7.2 months; (HR 0.71; 95% CI 0.59–0.86). OS rates at 48 months were 16.7% for pembrolizumab and 10.1% for CT (Bellmunt et al., 2017). In addition, the ORR was higher in patients who

Table 2
Comparison between chemotherapy plus immunotherapy trials (KEYNOTE-361 and IMvigor130) and immunotherapy trial DANUBE.

Strategy	Chemotherapy plus immunotherapy						Immunotherapy		
	KEYNOTE-361 (Powles et al., 2021)			IMvigor130 (Galsky et al., 2020)			DANUBE (Powles et al., 2020)		
N	1010			1213			~885		
Trial design	Open label			Double blinded			Open label		
Arms	Pembro + GC/CbG (CT) (A) Pembro (B) CT (C)			Atezo + CT (A) Atezo (B) Placebo + CT (C)			Durva + treme (A) Durva (B) CT (C)		
Primary endpoints	PFS, OS (ITT) A vs. C			PFS, OS (ITT) A vs. C OS (ITT) B vs. C only formally tested if above OS is positive			OS (ITT) A vs. C OS (PD-L1 high) B vs. C		
Patient characteristics	Platinum eligible 47% PD-L1 +			Platinum eligible 24% PD-L1 +			Platinum eligible 60% PD-L1 +		
	Pembro+CT vs. CT	**Pembro vs. CT**		**Atezo+CT vs. CT+placebo**	**Atezo vs. CT+placebo**		**Durva+treme vs. CT**	**Durva vs. CT**	
mOS	**ITT = 17 vs. 14.3 mo, HR 0.86 not sig (±)**	ITT = 15.6 vs. 14.3 mo, HR 0.92 not sig PD-L1 high = 16.1 vs. 15.2 mo, HR 1.01 not sig		**2IA mOS (ITT) = 16.1 vs. 13.4 mo, HR 0.84 not sig (±)**	IA mOS (ITT) = 15.7 vs. 13.1 mo, HR 1.02 Interim mOS (PD-L1 +) = NE vs. 17.8 mo, HR 0.68 (#)		**ITT = 15.1 vs. 12.1 mo, HR 0.85 not sig (±)** PD-L1 high = 17.9 vs. 12.1 mo, HR 0.74 sig	ITT = 13.2 vs. 12.1 mo, HR 0.99 not sig **PD-L1 high = 14.4 vs. 12.1 months, HR 0.89 not sig (±)**	
mPFS	**ITT = 8.3 vs. 7.1 mo, HR 0.78 not sig (±)**	3.9 vs. 7.1 mo HR 1.32 sig		**ITT = 8.2 vs. 6.3 mo, HR 0.82 sig (±)**	ITT = 8.2 vs. 6.3 mo, HR 0.82 PD-L1 high = NE, HR 0.68		ITT = 3.7 vs. 6.7 mo PD-L1 high = 4.1 vs. 5.8 mo	ITT = 2.3 vs. 6.7 mo PD-L1 high = 2.4 vs. 5.8 mo	
ORR	ITT = 54.7% vs. 44.9% not sig	ITT = 30.3% vs. 44.9% not sig		ITT = 47% vs. 44% not sig	ITT = 23% vs. 44%		ITT = 36% vs. 49% PD-L1 high = 47% vs. 48%	ITT = 26% vs. 49% PD-L1 high = 28% vs. 48%	
Second-line	**Pembro + CT**	**Pembro**	**CT**	**Atezo + CT**	**Atezo**	**CT + placebo**	**Durva + Treme**	**Durva**	**CT**
Subsequent treatment	35.3%	41%	61.6%	26.2%	39.8%	41%	45%	47%	54%
Immunotherapy	6.6%	4.6%	48%	4.6%	2.6%	20.4%	5%	3%	31%

(#) Not formally tested. (±) primary endpoint.
2IA: second interim analysis; Atezo: atezolizumab; C: cisplatin; Cb: carboplatin; CT: chemotherapy; Durva: durvalumab; G: gemcitabine; IA: interim analysis; ITT: intention-to-treat; m: median; mo: month; PD-L1: programmed death-ligand 1; Pembro: pembrolizumab; PFS: progression-free survival; sig: statistically significant; Treme: tremelimumab; ORR: objective response ratio; OS: overall survival.

received pembrolizumab (21.9% vs. 11%) and median DOR for responders was longer for pembrolizumab vs. CT (29.7 months vs. 4.4 months) (Bellmunt et al., 2017; Bellmunt et al., 2021). The second study, the IMvigor211, which randomly assigned 931 patients to atezolizumab or CT, failed to achieve its primary objective of improving survival in the IC2/3 population (n = 234) in a hierarchical design (median 11.1 months vs. 10.6 months (HR 0.87; 95% CI 0.63–1.21), thus precluding further formal statistical analysis. Despite this, atezolizumab maintained its approval for second-line use (Powles et al., 2018). More recently, the accelerated approvals of atezolizumab and durvalumab were voluntarily withdrawn by the responsible companies in the United States following the failure of the confirmatory phase III trials (IMvigor211 and DANUBE) (Powles et al., 2018; Powles et al., 2020; Slater, 2022; Sternberg, 2022).

In addition to immunotherapy treatments, other new drugs are being developed. Those directed against FGFR, such as erdafitinib, have achieved an ORR of 40% in a phase II study of patients with mUC and *FGFR* genetic alterations after treatment with platinum-based CT and, in many cases, after treatment with CPI (Loriot et al., 2019). Among the 22 patients who had previously received immunotherapy, the ORR was 59% (Loriot et al., 2019). In 2019, the FDA granted accelerated approval for erdafitinib in patients with locally advanced or mUC, with susceptible *FGFR3* or *FGFR2* genetic alterations, that has progressed during or following platinum-containing CT, including within 12 months of neoadjuvant or adjuvant platinum-containing CT (Food and Drug Administration, 2022d). A randomized phase III clinical trial to evaluate efficacy of erdafitinib versus vinflunine, docetaxel or pembrolizumab (based on prior CPI treatment) in patients with mUC harboring selected *FGFR* aberrations who have progressed after 1 or 2 prior treatments, is currently ongoing, and its results will refine the role of erdafitinib in these patient populations (NCT03390504).

Additionally, several other drugs targeting the FGF-FGFR signaling pathway, including small molecule FGFR tyrosine kinase inhibitors, FGFR antibodies, FGF ligand traps, and ADCs are being actively tested in mUC in first and subsequent lines both as single agents or in combinations (Garje et al., 2020).

ADC therapies such as EV have shown efficacy in pretreated patients with locally advanced or metastatic disease. The phase III trial EV-301 randomly assigned 608 patients who had previously received platinum-containing CT and whose disease had progressed during or after treatment with an anti-PD-L1/PD-1 to receive EV or investigator of choice CT (taxanes or vinflunine) (Powles et al., 2021). At the prespecified interim analysis, the median follow-up was 11.1 months. The primary OS endpoint was longer in the EV group than in the CT group (median OS 12.88 vs. 8.97 months; HR 0.70; 95% CI 0.56–0.89). PFS was also longer in the EV group than in the CT group (median PFS 5.55 vs. 3.71 months; HR 0.62; 95% CI 0.51–0.75). ORR was also significantly higher in the EV arm (40.6% vs. 17.9%, of which 4.9% and 2.7% were CR, respectively). The incidence of treatment-related adverse events was similar in the two groups as well as the incidence of events of grade ≥ 3 (Powles et al., 2021). Patients receiving EV had numerically less deterioration and variability in quality of life during the first 12 weeks of treatment than patients in the CT group (Mamtani et al., 2021). Additionally, the results from the cohort 2 of the phase II study EV-201, which included 89 patients with locally advanced or mUC with progression on a prior CPI in the upfront setting, showed an ORR of 52%

with 20% CR and a median DOR of 10.9 months. Median PFS and OS were 5.8 months and 14.7 months, respectively (Yu et al., 2021). In July 2021, the FDA granted regular approval for EV based on the results of the above studies, for adult patients with locally advanced or mUC who have previously received a PD-L1/PD-1 inhibitor and platinum-containing CT or are ineligible for cisplatin-containing CT and have previously received one or more prior lines of therapy (Food and Drug Administration, 2022e).

Another ADC is SG, a Trop-2-directed ADC to a topoisomerase I inhibitor (SN-38). Data from the cohort 1 of the phase II TROPHY-U-01 study, which included 113 patients with mUC previously treated with platinum-based CT and anti-PD-L1/PD-1 therapy, showed an ORR of 27% (5% had CR). The median PFS was 5.4 months, and the median OS was 10.5 months (Loriot et al., 2020). TROPiCS-04 is an ongoing phase II multicenter, open-label, randomized, controlled trial in patients with locally advanced unresectable or mUC who progressed after prior platinum-based and CPI therapies. Approximately 482 patients will be randomized to receive SG or CT of choice (Grivas et al., 2021). In April 2021, the FDA granted accelerated approval for SG in patients with locally advanced or mUC who previously received a platinum-containing CT and either a PD-L1/PD-1 inhibitor (Food and Drug Administration, 2022f). Table 3 shows a summary of the efficacy data for all these treatments.

3. Molecular and genetic markers

In the current treatment scenario of mUC with different drugs recently approved, the identification of valid predictive biomarkers remains of paramount importance to maximize treatment benefit and minimize detrimental effects.

3.1. Predictive biomarkers for checkpoint inhibitors

PD-L1 protein expression in either tumor or immune cells was proposed early on as a potential biomarker of response to CPIs based on the mechanisms of action of these drugs. More than 80% of the CPI pivotal trials in different tumors had PD-L1 expression as a correlate. However, only 28.9% of the 45 studies confirmed a predictive role for PD-L1 and 9 FDA regulatory approvals required companion PD-L1 diagnostic testing (Davis and Patel, 2019).

In mUC, the predictive value of PD-L1 expression has been inconsistent. In platinum-refractory patients, higher levels of PD-L1 in infiltrating immune cells correlated with better ORR in early studies with atezolizumab (Rosenberg et al., 2016; Powles et al., 2014). However, in a confirmatory phase III trial (IMvigor211), high PD-L1 expression did not predict greater benefit of atezolizumab versus CT (Powles et al., 2018). Likewise, the initial development of pembrolizumab focused on mUC with PD-L1 expression $\geq$ 1% in tumor cells or stroma (Plimack et al., 2017), however the pivotal randomized phase III trial in mUC platinum-refractory patients (KEYNOTE-045) showed pembrolizumab OS benefit when compared to CT irrespective of PD-L1 status (Bellmunt et al., 2017). Furthermore, atezolizumab and pembrolizumab were initially approved in the frontline setting in cisplatin-ineligible PD-L1-positive patients. An exploratory analysis of the confirmatory phase III trial IMvigor130 suggested an improved OS with atezolizumab monotherapy versus CT in cisplatin-ineligible patients PD-L1-positive (Galsky et al., 2021). Conversely, a similar analysis in the KEYNOTE-361 trial suggested that PD-L1 CPS did not predict outcome with pembrolizumab in cisplatin-ineligible patients (Powles et al., 2021), leading the FDA to modify the present label for pembrolizumab, limiting it to platinum ineligible patients independently of PD-L1 expression.

In the phase III JAVELIN Bladder 100 study, avelumab maintenance benefited patients regardless PD-L1 biomarker (40). Furthermore, several exploratory biomarkers were evaluated including PD-L1, tumor mutational burden (TMB), mutation profile, and genetic signatures (Powles et al., 2020). The PD-L1-positive population was investigated as a co-primary endpoint in a pre-specified analysis and revealed a potentially greater benefit for PD-L1 expressing patients (HR 0.56 vs. 0.69 in the entire population). Nevertheless, PD-L1 expression was associated with survival irrespective to the treatment arm and since it was not a stratification factor, further conclusions cannot be reached, remaining elusive the prognostic value of PD-L1 in this setting. Further analyses also suggest that PD-L1 expression alone did not fully predict OS benefit (Powles et al., 2021). When TMB was analyzed, the median number of non-synonymous mutations (7.66 mutations/Mb) was used to define patient subgroups. Patients with TMB above this threshold showed a greater OS benefit with avelumab despite being PD-L1 negative (HR 0.44). Conversely, tumors with low TMB but PD-L1 positive benefited from avelumab (HR 0.60). Therefore, it may be concluded that neither the biomarkers, TMB nor PD-L1 status individually, are sufficient to properly select patients most likely to benefit from therapy. The type of mutational process (mutational signature) was also analyzed. An apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) mutational signature that caused a cytosine to thymine transition as well as mutations located in DNA damage response and repair genes, showed greater benefit from avelumab. Furthermore, gene expression analysis showed that a higher expression of immune modulation-related genes related to innate and adaptive effector cells (CD8, CXCL9, IFNG, LAG3, and TIGIT) correlated with better outcomes in patients who received avelumab. Lastly, immune gene signatures previously developed in other tumor types were explored in JAVELIN Bladder 100 patients, which showed some discriminatory capacity and were also able to identify alternative mechanisms of resistance that might involve a network of tumor supporting pathways, such as tumor growth factor beta and angiogenesis (Powles et al., 2021). Whereas no

Table 3
Current treatments for the second-line approach in locally advanced disease.

Drug	Trial	N	Phase	Line	ORR	CRR	OS, months
Docetaxel (McCaffrey et al., 1997; Petrylak et al., 2017)		30	II	$\geq$ 2nd Line	13%		9
Paclitaxel (Vaughn et al., 2002; Joly et al., 2009)		31	II	2nd Line	10%		7
Vinflunine (de Santis et al., 2009)	V vs. BSC	37	III	2nd Line	9%		6.9
Nivolumab (Sharma et al., 2017; Sharma et al., 2016)	CheckMate 032	78	I/II	$\geq$ 2nd Line	24%	6%	9.7
	CheckMate 275	270	II	2nd Line	20%	3%	8.6
Atezolizumab (Rosenberg et al., 2016; Powles et al., 2018)	IMvigor210	310	II	$\geq$ 2nd Line	16%	7%	7.9
	IMvigor211		III vs. CT	$\geq$ 2nd Line	13%	3%	8.6
Pembrolizumab (Plimack et al., 2017; Bellmunt et al., 2017)	KEYNOTE-012	27	II	$\geq$ 2nd Line	26%	11%	13
	KEYNOTE-045	542	III vs. CT	$\geq$ 2nd Line	21.1%	8%	10.3
Durvalumab (Massard et al., 2016)	MEDI4736	41	I	$\geq$ 2nd Line	31%		NR
Avelumab (Apolo et al., 2017)	JAVELIN Solid Tumor	249	II	$\geq$ 2nd Line	16%	5%	7.7
Erdafitinib (Loriot et al., 2019)	BLC2001	99	II	$\geq$ 2nd Line	40%	3%	13.8
Enfortumab vedotin (Powles et al., 2021)	EV301	608	III	3rd Line	40.6%	4.9%	12.9
Sacituzumab govitecan (Loriot et al., 2020)	TROPHY-U01	113	II	3rd Line	27%	5%	10.5

BSC: best supportive care; CRR: complete response rate; CT: chemotherapy; OS: overall survival; ORR: objective response rate.

molecular biomarker has been validated to predict benefit from avelumab maintenance until now, candidate patients were selected by no progression on prior platinum-based CT, which has been proposed as a putative clinical marker to identify a group of patients who may benefit from avelumab maintenance (Grivas et al., 2021). More recently, The Cancer Genome Atlas (TCGA) genomic subgroups have been evaluated as potential predictors of benefit in a post-hoc analysis of JAVELIN Bladder 100 trial. The survival benefit for avelumab was apparent across TCGA subtypes except luminal. Yet, the small sample size and the wide CI limit any practical conclusion (Powles et al., 2021).

3.2. Biomarkers to other targeted agents

EV and SG are ADCs that bind proteins Nectin-4 and Trop-2 respectively, which have been reported to be widely expressed in UC both in bladder cancer and upper genitourinary tract tumors and therefore no prior testing would be necessary (Stepan et al., 2011; Challita-Eid et al., 2016; Rosenberg et al., 2020). Heterogeneity of expression of Nectin-4, Trop-2, and other targets has been reported in variant histologies (i.e. small cell, carcinosarcoma, etc.) with low or null expression and this may have therapeutic implications (Hoffman-Censits et al., 2020). Nectin-4 and Trop-2 expression have been confirmed as negative prognostic biomarkers in several tumors, including UC (Tomiyama et al., 2020).

FGFR could probably be considered the only fully validated predictive biomarker in mUC therapeutics as discussed above. *FGFR* presents aberrations in about 15–20% of mUC cases, with these gene abnormalities exceeding 40–50% in upper tract UC (Rodríguez-Vida et al., 2015; Li et al., 2016). Recent data from a mUC biomarker driven study revealed that tumors with *FGFR* alterations had a low prevalence of PD-L1 expression and TMB. Analysis of mRNA expression revealed an increased proportion of the luminal papillary subtype in tumors with *FGFR* alterations but not a higher expression of immune-active T-cell signatures (Powles et al., 2021). These findings might have a potential predictive value although data are still not consistent and require further validation.

4. Current treatment guidelines

NCCN Guidelines Version 5.2021 recommends first-line cisplatin-based CT (GC or ddMVAC with growth factor support in selected patients) followed by avelumab maintenance therapy in those patients not progressing with first-line CT, as the preferred regimen (category 1) (NCCN Guidelines®, 2021). In cisplatin-ineligible patients, preferred regimens are CbG followed by avelumab maintenance therapy (category 1) if there is no progression to first-line CT. Atezolizumab is recommended in cisplatin-ineligible patients only if their tumors express PD-L1 or if they are not eligible for any platinum-containing CT regardless of PD-L1 expression (category 2 A). P(NCCN Guidelines®, 2021).

For second-line systemic therapy in patients who progress on platinum-based CT, the preferred regimen is pembrolizumab (category 1). Alternative preferred regimens include other CPIs (nivolumab or avelumab), erdafitinib or EV (if available) (category 2 A). Other recommended regimens include paclitaxel, docetaxel or gemcitabine (category 2 A). In patients who progress after CPIs, the preferred regimen for cisplatin-ineligible and CT-naïve patients is CbG or EV if available (Yu et al., 2021), and for cisplatin-eligible CT naïve patients it is GC or ddMVAC with growth factor support (category 2 A) (NCCN Guidelines®, 2021). For the next line of systemic therapy in locally advanced or metastatic disease, the preferred regimen is EV (category 1) or erdafitinib in patients with susceptible *FGFR3* or *FGFR2* genetic alterations (category 2 A) (NCCN Guidelines®, 2021).

In the ESMO guidelines, platinum-based CT is recommended for advanced or mUC (I, A). GC or CbG are the most widely used regimens. In patients who have not progressed following 4–6 cycles of first-line platinum-based CT, maintenance avelumab started within 10 weeks maximum of completion of CT is recommended (I, A; MCBS 4). Pembrolizumab or atezolizumab are alternative choices for the first-line in cisplatin-ineligible metastatic patients who are PD-L1-positive (III, B) (Powles et al., 2021). Platinum-based CT followed by maintenance avelumab is preferential compared with upfront CPIs in PD-L1 biomarker-positive patients. No consensus could be reached for CPIs in PD-L1 biomarker-negative patients not eligible for any CT (Powles et al., 2021).

In patients with platinum-refractory disease CPIs are standard options: pembrolizumab (I, A; MCBS 4), atezolizumab (II, B), nivolumab (III, B), avelumab (III, C), and durvalumab (III, C). Treatment with CT is an alternative for patients in whom CPIs are not possible. Vinflunine (II, C), docetaxel (III, C), and paclitaxel (III, C) can be considered. Combinations with taxanes may be considered as an option only in selected patients. Erdafitinib (not currently EMA-approved) is an option in platinum-refractory or platinum- and CPI-refractory UC tumors with selected *FGFR2* or *FGFR3* alterations (III, B). EV is recommended in patients with platinum- and CPI-refractory UC (I, A; MCBS 4) or after relapse to first-line CPI (III, B) as alternative to CT (Powles et al., 2021).

The European Association of Urology (EAU) guidelines, published in September 2021, are in agreement with the above ESMO guidelines (Cathomas et al., 2022).

5. Proposal for a new treatment algorithm for patients with metastatic urothelial carcinoma

Based on the current evidence, the different therapeutic options for the treatment of patients with UC are summarized in Fig. 2. Due to the continuous advances in diagnosis, surgical techniques, radiotherapy, medical treatments and clinical trials, a multidisciplinary approach is recommended to design the most appropriate strategy for every patient, taking into consideration the stage of the disease, the comorbidities and circumstances of the patient, and the resources available in each center.

6. Questions remaining for the future

Avelumab first-line maintenance is the new SoC in patients with no progression on platinum-based CT regardless of PD-L1 status. Despite the improvement in OS and PFS shown in the JAVELIN Bladder 100 trial, 37% of patients had disease progression as best response in the avelumab plus BSC arm. Novel therapeutic approaches combining avelumab with other drugs in the first-line maintenance setting are under development (TALASUR study with talazoparib/NCT04678362; MAIN-CAV study with cabozantinib/NCT05092958; PRESERVE3 study with trilaciclib/NCT04887831) to further improve the benefit seen in the JAVELIN Bladder 100 trial. Longer follow-up and additional analysis may provide some information and help to identify those patient populations who benefit the most from avelumab maintenance. Furthermore, it remains questioned whether avelumab maintenance may be an option for patients with no progression on less than the 4 platinum-based CT cycles (i.e. $\leq$ 3 cycles) in the first-line setting. The findings from the DISCUS trial will provide some clarity on this regard (Powles, 2022). Clinical data with avelumab maintenance after prior CPIs in the neoadjuvant or adjuvant setting will be interesting to have in the face of the arrival of CPIs into the perioperative setting. Another scenario where no data are available with CPI maintenance is in the second-line setting after CR, PR, or SD with a platinum-based CT after progression on frontline CPI monotherapy. The treatment sequence after progression on avelumab maintenance also remains to be clarified; based on the information of subsequent lines from the JAVELIN Bladder 100 trial, CT, platinum-based CT rechallenge and targeted therapies can be used (Grivas et al., 2021). EV and erdafitinib are reasonable alternatives as they have already shown efficacy in mUC after progression to platinum-based CT and/or CPI monotherapy and have also been used as a subsequent line of therapy after progression on avelumab maintenance

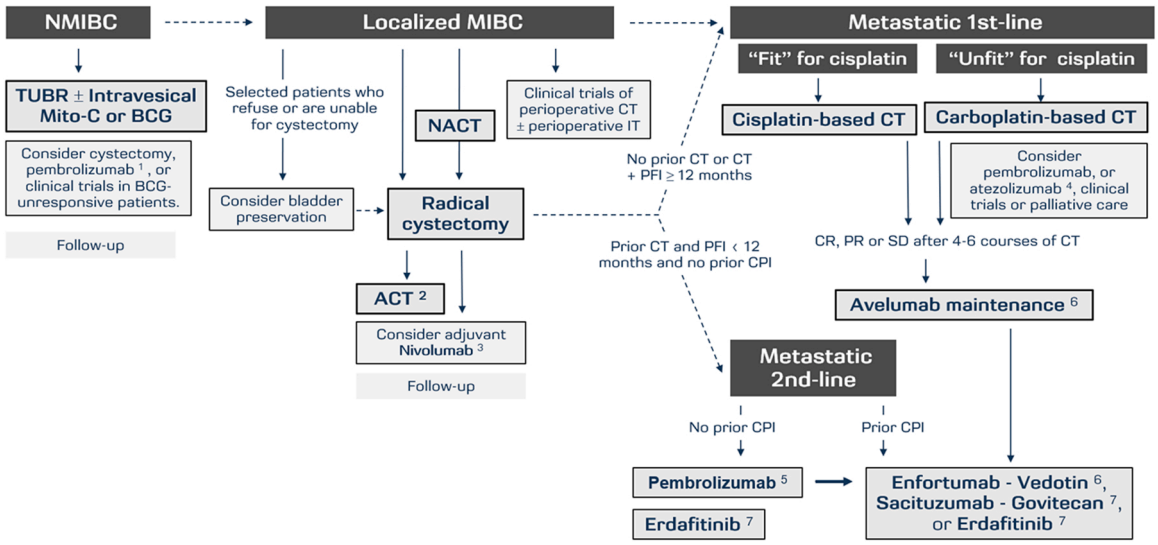

Fig. 2. Therapeutic options and comprehensive approach for the patient with bladder carcinoma. ACT: adjuvant chemotherapy; BCG: Bacillus Calmette-Guérin; CR: complete response; CT: chemotherapy; CPI: immune checkpoints inhibitors; IT: immunotherapy; NACT: neoadjuvant chemotherapy; NMIBC: non-muscle invasive bladder carcinoma; MIBC: muscle invasive bladder carcinoma; Mito-C: Mitomycin C; PFI: platinum-free interval; PR: partial response; SD: stable disease; TURTB: transurethral resection of bladder tumor. 1. Licensed by FDA for BCG-unresponsive NMIBC patients; 2. For patients who have not received neoadjuvant chemotherapy; 3.Nivolumab has been licensed by FDA as adjuvant therapy for MIBC in patients who had pT2-pT4 or pN+ after NACT, or pT3–4a or pN+ after cystectomy without previous NACT, and refuse, or are not eligible for ACT; 4. Pembrolizumab and atezolizumab have been approved by FDA and EMA for patients with PDL1 + expression (see text for details) and may be an option for patients unable to receive CT (pembrolizumab recently restricted by FDA for patients unable to receive CT); 5. Nivolumab and atezolizumab are also approved by EMA, and nivolumab and avelumab by FDA for second-line after platinum-based CT. No data available in patients with prior CPI; 6. FDA and EMA approved; 7. FDA approved; 8. FDA approved in patients with altered FGFR. See text for further details and references.

in the pivotal trial.

7. Summary

- With the aim of bringing treatment with immunotherapy into earlier lines and offer these active therapies to more patients with advanced UC, different therapeutic approaches have been developed in the upfront setting, including the use of CPIs as single agents, combinations of CPIs ± CT or ADC and the use of CPIs as maintenance after non-progression with first-line CT.
- The phase III JAVELIN Bladder 100 trial was designed with the aim of extending the initial benefit achieved with first-line platinum-based CT by adding avelumab maintenance in patients that had not progressed to CT.
- According to the NCCN, ESMO and EAU treatment guidelines, rapid introduction of avelumab maintenance in patients that have not progressed with platinum-based CT is a preferred option over a treatment break or treatment with a CPI in second-line since it has shown a statistically significant improvement in OS versus BSC, with the longest OS ever achieved in a phase III trial in mUC, and may also enable more patients to receive a CPI rather than reserving it to the second-line. Avelumab maintenance does not require PD-L1 testing for treatment selection as the benefit is observed regardless of PD-L1 status. Based on single-arm phase II trials, first-line treatment with atezolizumab or pembrolizumab are alternatively choices in Europe only for cisplatin-ineligible patients with PD-L1 positive tumors or if they are not eligible for any platinum-containing CT (FDA only).

- Unlike other solid tumors such as lung cancer, currently there is no evidence supporting the use of the combination of CPIs and CT as first-line therapy in mUC and this strategy is not currently recommended. First-line phase III chemo-immunotherapy trials (IMvigor130 and KEYNOTE-361) have recently been published with disappointing results.
- ADCs such as EV and SG, which target specific proteins expressed in UC cells, have shown promising activity as single agent in subsequent lines of treatment. Moreover, the combination of EV with pembrolizumab is being currently tested in a randomized phase III study in the upfront setting (EV-302 trial) based on the remarkable activity from the phase I/II trial (EV-103 study).

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