Current Oncology Reports (2018) 20:48
https://doi.org/10.1007/s11912-018-0693-y

GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Emerging Role of Immunotherapy in Advanced Urothelial Carcinoma

Vadim S. Koshkin[1] · Petros Grivas[2]

Abstract

Purpose of Review Advanced urothelial carcinoma (aUC) has long been treated preferably with cisplatin-based chemotherapy, but many patients are cisplatin-ineligible whereas for those who progress on a platinum-based regimen treatment options are limited. We review key recent data regarding immune checkpoint inhibitors that are changing this treatment landscape.

Recent Findings Since May 2016, five different agents targeting the PD-1/PD-L1 pathway (atezolizumab, pembrolizumab, nivolumab, avelumab, durvalumab) have received FDA approval for the treatment of aUC in the platinum-refractory setting, while pembrolizumab and atezolizumab are FDA-approved for cisplatin-ineligible patients in the first-line setting. Clinical outcomes and safety profiles of these agents appear relatively comparable across separate trials; however, only pembrolizumab is supported by level I evidence from a large randomized phase III trial showing overall survival benefit over conventional cytotoxic salvage chemotherapy in the platinum-refractory setting.

Summary Pembrolizumab has the highest level of evidence in platinum-refractory aUC, whereas pembrolizumab and atezolizumab have comparable level of evidence in the frontline setting in cisplatin-ineligible patients. Ongoing research is evaluating novel agents, various rational combinations, and sequences, as well as predictive and prognostic biomarkers.

Keywords Metastatic bladder cancer · Advanced urothelial carcinoma · Immunotherapy · Immune checkpoint inhibitors · PD-1 · PD-L1 · Cisplatin-ineligible · Platinum-refractory · Atezolizumab · Pembrolizumab · Avelumab · Nivolumab · Durvalumab · Biomarkers · clinical trials

Introduction

Bladder cancer is a common malignancy with more than 79,000 new cases and almost 17,000 deaths predicted to occur in 2017 only in the USA [1]. It is the 6th most commonly diagnosed malignancy in the USA and the 4th most common in men, while being the most expensive cancer to treat from diagnosis to death [2]. Urothelial carcinoma is the most common bladder cancer histology, although a number of other histological variants with probably distinct biology including adenocarcinoma, squamous cell carcinoma, and small cell carcinoma are also encountered in clinical practice [3]. Urothelial carcinomas can arise in the entire urinary tract, including ureters, renal pelvis, and urethra, but most commonly in bladder.

A high number of patients with non-muscle invasive bladder cancer (NMIBC) are managed with transurethral bladder tumor resection (TURBT) and intra-vesical therapy, such as Bacillus Calmette-Guerin (BCG), and less commonly intravesical chemotherapy. Additionally, a number of clinical trials are ongoing, especially in the BCG-relapsing and BCG-refractory settings. For patients with muscle invasive bladder cancer (MIBC) and advanced/metastatic urothelial carcinoma (aUC), the outcomes are considerably inferior compared to NMIBC. The 5-year survival for patients with MIBC is overall less than 50% and depends mostly on stage, received treatments and response to those [4]. For patients with aUC, median overall survival (OS) has been in the range of about 15 months with the current frontline standard of cisplatin-based chemotherapy [5]. Although about 10–15% of aUC patients are alive beyond 5 years following cisplatin-based

This article is part of the Topical Collection on *Genitourinary Cancers*

✉ Petros Grivas
pgrivas@uw.edu

Vadim S. Koshkin
koshkiv@ccf.org

[1] Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave, Desk CA-60, Cleveland, OH 44195, USA

[2] Department of Medicine, Division of Oncology, Seattle Cancer Care Alliance, University of Washington and Fred Hutchinson Cancer Research Center, 825 Eastlake Ave E, MS: G4-830, Seattle, WA 98109, USA

Published online: 11 April 2018

chemotherapy and can be considered cured (mostly those with only regional lymph node metastasis), most of the treated patients with aUC will ultimately succumb to their disease. An additional significant consideration is that many patients with urothelial carcinoma are often diagnosed at an advanced age, may have significant comorbidities, and compromised performance status (PS) that can preclude treatment with cisplatin-based regimens [6]. Treatment options for this patient population considered cisplatin-ineligible are more limited and outcomes often inferior.

In recent years, significant advances in the understanding of underlying tumor and host biology and immunology have revolutionized the treatment of many advanced solid malignancies including urothelial carcinoma. Improved understanding of the mechanisms that allow tumors to escape immune surveillance has led to the development of immune checkpoint inhibitors (ICIs). These agents upregulate anti-tumor immune response leading to significant anti-tumor activity in a significant number of aUC patients refractory to prior platinum (cisplatin or carboplatin) therapy. They have additionally shown efficacy as frontline therapy in clinical trials of cisplatin-ineligible patients. This review summarizes key data from recent clinical trials of immunotherapy agents in aUC after describing the role of platinum-based chemotherapy. It additionally discusses ongoing clinical trials that aim to maximize response to ICIs, including combination therapies, optimal sequences, and efforts on putative prognostic and/or predictive biomarkers.

Historical Data with Chemotherapy

Platinum-based chemotherapy has been the standard of care in aUC for the past couple of decades. A clinical trial of the classical (conventional) MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen in 92 patients in the 1980s showed an objective response rate (ORR) of 69% and complete responses (CR) in 37% [7]. When prospectively compared to cisplatin monotherapy in 246 patients, MVAC regimen showed superior OS (12.5 vs 8.5 months), progression-free survival (PFS) (10 vs 4.3 months), and ORR (39 vs 12%) [8]. Various adjustments to the classical MVAC regimen have subsequently been implemented due to significant toxicities associated with this regimen. A regimen of dose-dense MVAC (ddMVAC) administered in 2-week rather than 4-week cycles with growth-factor support was compared to classical MVAC in the EORTC 30924 phase III trial that included 263 patients. The ddMVAC had more favorable toxicity profile and higher ORR (62 vs 50%, $p = 0.06$) while having comparable median OS (15.1 vs 14.9 months) [9, 10]. Another commonly used regimen for aUC is GC (Gemcitabine/Cisplatin) administered typically in a 3-week rather than a 4-week cycle. A randomized phase III trial of 405 patients comparing GC with classical MVAC regimen given for up to 6 cycles showed better toxicity profile with GC and comparable ORR, PFS, and OS in the two arms [5, 11]. A prospective comparison of ddMVAC and dose-dense GC (ddGC, given every 2 weeks) that included 130 patients showed improved tolerability of treatment in the ddGC arm with more patients completing 6 cycles of treatment. OS was comparable at 19 months for ddMVAC and 18 months for ddGC as was PFS (8.5 vs 7.8) [12]. The current NCCN recommendations for aUC patients who are eligible to receive cisplatin-based chemotherapy include either GC or ddMVAC with growth-factor support in the frontline treatment-naïve setting with most patients getting up to 6 cycles (with interim imaging to assess response).

Patients with aUC who are cisplatin-ineligible are defined according to criteria put forth by a consensus expert panel which include at least one of the following: ECOG PS of 2, estimated creatinine clearance < 60 ml/min (although many experts use lower cutoff, e.g., 50 ml/min and may include 24-h urine collection for better estimation in borderline cases), ≥ grade 2 peripheral neuropathy, ≥ grade 2 hearing loss, class III NYHA heart failure [6]. The standard of care in this patient population has included carboplatin-based regimens. A comparative analysis of four randomized trials and 286 patients with aUC that compared cisplatin and carboplatin-based regimens found superior ORR and CR with cisplatin-based regimens [13]. Among cisplatin-ineligible patients, EORTC 30986 was a large randomized phase II/III trial that enrolled 238 patients with impaired renal function or ECOG PS 2. Patients were randomized to receive either gemcitabine/carboplatin or methotrexate/carboplatin/vinblastine. In general, gemcitabine/carboplatin treatment was better tolerated with no significant differences in efficacy noted among the two groups with ORR at 30–41% and OS at 8.1–9.3 months [14, 15]. Therefore, gemcitabine/carboplatin is commonly used in the first-line setting in cisplatin-ineligible patients. Typically, patients receive 4–6 cycles of platinum-based chemotherapy in the frontline setting (based on interim response and tolerance) and afterwards are usually placed on observation until progression; however, two ongoing trials (NCT02603432; NCT02500121) are evaluating the concept of maintenance immunotherapy after no progression to first-line chemotherapy.

For aUC patients who progressed on platinum-based regimens, the options until very recently were quite limited. Multiple single-agent regimens including paclitaxel, docetaxel, gemcitabine, ifosfamide, and pemetrexed were attempted in the second-line setting with ORR generally in the 10% range and median OS in the 5–9-month range based mostly on data from single-arm phase II trials [16–20]. The largest trial, which enrolled 370 platinum-refractory aUC patients, randomized them in a 2:1 ratio to receive vinflunine plus best supportive care versus best supportive care alone [21]. The OS in the treated patients was slightly higher in the vinflunine arm

(6.9 vs 4.3 months) leading to its approval in this treatment setting in Europe; however, FDA approval in the platinum-refractory setting was not granted. Until May 2016, there were no FDA-approved second-line agents for the treatment of platinum-refractory aUC. The immune checkpoint inhibitors changed this landscape.

Immunotherapy in the Platinum-Refractory Setting

The most clinically active immune checkpoint inhibitors in aUC and other advanced solid malignancies that have been developed up to this point impact the programmed death-1 (PD-1) pathway. PD-1 is a protein expressed on the surface of T cells that interacts with multiple ligands, including programmed death-ligand (PD-L1, also known as B7-H1) and programmed death-ligand 2 (PD-L2, also known as B7-DC). PD-L1 is typically expressed on other immune cells, including antigen-presenting cells, as well as tumor cells. The interaction of PD-1 with its ligands leads to the inhibition of T cell activity and overall downregulation of the immune response [22]. This mechanism of immune-tolerance is hijacked by many tumors whose cells express PD-L1 and thus attenuate anti-tumor immune responses [23]. A class of anti-PD-1 and anti-PD-L1 antibodies were developed to counteract this interaction and thus enhance anti-tumor immune responses.

Atezolizumab

Atezolizumab (MPDL3280A) is a fully humanized monoclonal antibody against PD-L1. It was initially investigated in a urothelial carcinoma cohort of a phase Ia study (NCT01375842) that showed significant anti-tumor activity and durable responses in aUC patients previously treated with platinum-based chemotherapy [24]. Higher response rates were noted in tumors that had more PD-L1-positive tumor-infiltrating immune cells. These promising results led to it receiving a breakthrough designation status by the FDA in June 2014. A 2-year follow-up of these results was presented at the 2017 ASCO Meeting [25]. The primary endpoint of this trial was safety/tolerability and among 95 safety-evaluable patients grade 3/4 treatment-related adverse events (TRAEs) noted in 8% with no treatment-related deaths reported. Among 94 patients evaluable for response, ORR was 27% with 10% CR rate and the median duration of response was 22.1 months; median OS in this cohort was 10.6 months.

This positive signal led to the further development of atezolizumab in both platinum-refractory and cisplatin-ineligible frontline settings as part of IMvigor 210 phase II trial. This was a single-arm phase II study in patients with locally advanced or metastatic urothelial carcinoma that enrolled patients in two cohorts, both treated with atezolizumab. Cohort 1 enrolled first-line cisplatin-ineligible patients and will be discussed later. Cohort 2 enrolled patients who had progressed during or following platinum-containing regimen and enrolled 310 patients treated with atezolizumab 1200 mg IV every 3 weeks [26•]. Patients were stratified according to PD-L1 expression in immune-infiltrating cells as either IC0 (< 1%), IC1 (≥ 1 and ≤ 5%), or IC2/3 (≥ 5%). ORR for all patients was 15% with 5% CR rate. Among IC2/3 patients ($n = 100$), ORR was 26% while among IC0/1 patients ($n = 210$), it was 10%. Higher responses were additionally seen among patients with The Cancer Genome Atlas Project (TCGA) luminal II subtype and with higher mutational load [27]. Median OS in the entire cohort was 7.9 months and median PFS 2.1 months. Median time to response was 2.1 months and many responses were durable with 84% of responses ongoing at the time of data cutoff. Durable responses were recorded in patients with upper tract urothelial carcinoma and poor prognostic features, such as liver and visceral metastases. TRAEs were noted in 69% of patients with 16% having grade 3/4 TRAEs and no treatment-related deaths being recorded. Among 137 patients who continued atezolizumab beyond radiologic progression, 33% had subsequent reduction in tumor burden but only 3.6% of those had RECIST v1.1. responses compared to baseline; however, this subset of patients had fewer poor prognostic factors compared to those who did not continue atezolizumab beyond radiologic progression [28]. The data from this trial led to FDA granting accelerated approval to atezolizumab in May 2016 as salvage therapy for patients with metastatic urothelial carcinoma who had progression on or following platinum-based chemotherapy [29]. This was the first agent FDA-approved in this disease setting in over two decades.

The comparison of atezolizumab with chemotherapy in platinum-refractory patients with aUC was investigated in the phase III IMvigor 211 trial [30]. This trial randomized patients to receive atezolizumab 1200 mg IV every 3 weeks or investigator's choice of chemotherapy with either viflunine, paclitaxel, or docetaxel. The primary endpoint of OS was to be assessed hierarchically, first in patients with PD-L1 IC 2/3, then in IC 1/2/3 patients, and ultimately in the overall study population. Statistical significance had to be demonstrated in the first analysis among PD-L1 IC 2/3 patients in order to move on to subsequent analyses. In May 2017, Roche, the manufacturer of atezolizumab and sponsor of the trial announced that IMvigor 211 did not meet its primary endpoint among the IC 2/3 patients [31]. Subsequently published results from the IMvigor 211 trial showed that in the IC 2/3 population OS was not statistically different in the atezolizumab group compared to the chemotherapy group (11.1 vs 10.6 months; stratified HR 0.87; 95%CI 0.63–1.21, $p = 0.41$), which precluded further formal statistical analysis. The exploratory OS analysis in the intent-to-treat population showed median OS of 8.6 months with atezolizumab

compared to median OS of 8.0 months with chemotherapy (stratified HR = 0.85; 95%CI 0.73–0.99). Interestingly, median OS was longer in the population of higher PD-L1 tumor tissue "expressors" relative to the intent-to-treat population and the reason regarding this discordance with other ICI trials may be related to the PD-L1 assay used, which measures only tumor-infiltrating (and not tumor) cells [32]. The numerical advantage in OS in the intent-to-treat population for patients treated with atezolizumab relative to chemotherapy, as well as the better tolerability of atezolizumab, suggest benefit of this agent over salvage chemotherapy for platinum-refractory advanced urothelial carcinoma, despite the negative primary endpoint in the IMvigor211 trial. The ongoing IMvigor 130 trial (NCT02807636) is evaluating atezolizumab alone or combined with platinum (cisplatin or carboplatin)-gemcitabine chemotherapy compared to standard platinum-gemcitabine chemotherapy as first-line therapy in aUC.

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody against PD-1 whose safety and efficacy in aUC was first investigated in KEYNOTE-012, a multi-cohort phase Ib study [33]. Among 33 enrolled patients with aUC in this trial, ORR was 27% with 11% CR rate. No major adverse safety signals were observed, supporting the development of pembrolizumab in phase II and III studies in cisplatin-ineligible frontline setting and platinum-refractory setting. KEYNOTE-045 was a large open-label, international, phase III trial that randomized patients with platinum-refractory aUC to receive either pembrolizumab 200 mg IV every 3 weeks or investigator's choice of paclitaxel, docetaxel or vinflunine [34•]. A total of 542 patients were randomized and stratified according to ECOG PS, liver metastases, hemoglobin level, and time since last chemotherapy. The co-primary endpoints were OS and PFS assessed in all patients and patients who had PD-L1 combined positive score (CPS) ≥ 10 (percentage of tumor cells and infiltrating immune cells expressing PD-L1 relative to the total number of tumor cells). The trial met its primary endpoint with OS advantage with pembrolizumab of 10.3 vs. 7.4 months with chemotherapy (hazard ratio for death 0.73; 95% CI, 0.59–0.91, $p = 0.002$). Among patients with CPS ≥ 10 median OS was 8.0 months with pembrolizumab and 5.2 months with chemotherapy (hazard ratio 0.57; 95% CI, 0.37–0.88, $p = 0.005$). No PFS difference was noted between the two groups in the overall cohort or patients with CPS ≥ 10. Pembrolizumab was also better tolerated with fewer TRAEs of any grade (60.9 vs 90.2%) and fewer grade 3–5 TRAEs (15.0 vs 49.4%). The ORR was also higher with pembrolizumab (21.1%) compared to chemotherapy (11.4%). Although median time to response was identical in the two groups at 2.1 months, responses were more durable with pembrolizumab, with median response duration not reached at the time of analysis for pembrolizumab and 4.3 months with chemotherapy. Based on the results of this study, FDA granted pembrolizumab regular approval in May 2017 for patients with aUC refractory to platinum-based therapy [35]. Although this was the last among five checkpoint inhibitors to gain regulatory approval in this treatment space, pembrolizumab is the only agent that showed OS advantage over salvage chemotherapy in a randomized phase III trial, and consequently has become the new standard of care in the platinum-refractory setting. The ongoing Keynote 361 trial (NCT02853305) is evaluating pembrolizumab alone or combined with platinum (cisplatin or carboplatin)-gemcitabine chemotherapy compared to standard platinum-gemcitabine chemotherapy as first-line therapy in aUC.

Nivolumab

Nivolumab is an anti-PD1 antibody whose activity in aUC was initially investigated in CheckMate 032, a phase 1/2 multicenter trial in solid tumors. The trial included multiple cohorts including both nivolumab monotherapy and various dosage combinations of nivolumab with ipilimumab (an anti-CTLA-4 antibody). An interim analysis of the nivolumab monotherapy cohort was reported after 78 patients with platinum-refractory aUC were treated [36]. ORR was 24.4% with CR rate 6%. Grade 3–4 TRAEs were reported in 22% of patients. The overall activity and safety profile of nivolumab monotherapy in CheckMate 032 supported its further investigation in aUC and led to CheckMate 275 that was a phase II, multi-center, single-arm trial in platinum-refractory aUC patients treated with nivolumab 3 mg/kg IV every 2 weeks until progression or unacceptable toxicity [37•]. A total of 265 patients were evaluable for activity. In the overall cohort, ORR was 19.6% which included CR in 2% of patients. Among 81 patients with PD-L1 ≥ 5%, ORR was 28.4%. Responses were durable as median duration of response was not reached and 77% of patients had ongoing response at the time of analysis. Median PFS was 2.0 months and median OS 8.7 months. In the overall cohort, 26% of patients were treated with nivolumab beyond radiographic progression and 34% of those patients experienced clinical benefit. TRAEs of any grade occurred in 64% of patients and grade 3/4 TRAEs occurred in 18% of patients. Based on these results, in February 2017, the FDA granted accelerated approval to nivolumab at a dose of 240 mg IV every 2 weeks for patients with aUC refractory to platinum-based chemotherapy [38]. The ongoing Checkmate 901 trial (NCT03036098) is evaluating nivolumab/ipilimumab (anti-CTLA4) combination compared to standard platinum-gemcitabine chemotherapy as first-line therapy in aUC.

Durvalumab

Durvalumab is an anti-PD-L1 antibody that was initially investigated in aUC expansion cohort as part of a phase I/II trial

in metastatic solid tumors. Initial results were reported in 61 patients treated with durvalumab 10 mg/kg IV every 2 weeks for up to 12 months [39]. PD-L1 positivity was defined as ≥ 25% of tumor cells or tumor-infiltrating-immune cells expressing PD-L1. The primary endpoint was safety and therapy was very well tolerated as only 4.9% of patients experienced grade 3 TRAEs, while no grade 4–5 TRAEs were observed. In 42 response-evaluable patients, ORR was 31%. All responses were seen in PD-L1-positive patients. Updated results from this cohort were presented at the 2017 ASCO meeting [40•]. Among 191 treated patients with longer follow-up, ORR was 17.8% including 3.7% CR rate. Among patients with higher PD-L1 expression, ORR was 27.6%. Median time to response was 1.5 months and duration of response was not reached. Median PFS was 1.5 months and median OS 18.2 months. Grade 3/4 TRAEs occurred in 6.8% of patients. With this encouraging data, durvalumab was granted accelerated approval by the FDA in May 2017 for patients with platinum-refractory aUC [41]. Further development of durvalumab is being advanced by the phase III DANUBE trial (NCT02516241). This is a randomized multi-center trial comparing durvalumab alone, durvalumab/tremelimumab (anti-CTLA-4), and standard of care gemcitabine with either cisplatin or carboplatin chemotherapy as first-line therapy in aUC [42]. Various combinations of durvalumab with targeted therapies based on biomarker-based patient allocation is being tested in the ongoing phase Ib BISCAY "umbrella" trial (NCT NCT02546661) in platinum-treated patients with aUC.

Avelumab

Avelumab is an anti-PD-L1 antibody which was initially assessed in the JAVELIN trial, a phase I multi-cohort trial in solid tumors. In phase Ib expansion cohorts including the aUC cohort, a dose of 10 mg/kg IV every 2 weeks was used, based on the results from phase Ia dose-escalation study [43]. Phase Ib aUC cohort included 44 patients with platinum-refractory disease and primary objectives were safety and tolerability. After median follow-up of 16.5 months, grade 3/4 TRAEs were noted in only 6.8% of patients. ORR was 18.2% including CR rate 11.4%. Median duration of response was not reached and 75% of patients had ongoing response at the time of analysis. PD-L1 positivity in this trial was defined as ≥ 5% PD-L1 expression, and 7 of 8 responding patients had PD-L1-positive tumors. Median PFS was 11.6 weeks (2.7 months) and median OS was 13.7 months [44]. The results of a pooled analysis of two aUC cohorts including both platinum-refractory and cisplatin-ineligible patients have also been published. This analysis included a total of 241 patients treated with avelumab 10 mg/kg IV every 2 weeks. Among 153 patients with ≥ 6-month follow-up confirmed ORR 17.6% including 6.8% CR rate and another 23.5% had stable disease. Among PD-L1-positive tumors, ORR was 25%. Median duration of response was not reached, but the 24-week response rate was 92% in responders. Median PFS was 1.5 months and median OS 7.0 months. Grade 3/4 TRAEs occurred in 7.5% of patients [45]. An update of this pooled analysis summarizing treatment outcomes in 161 post-platinum patients with ≥ 6 months of follow-up reported similar results [46•]. Based on the results in the platinum-refractory cohort, avelumab was granted accelerated approval by the FDA in May 2017 for patients with aUC who progressed on prior platinum-based regimen [47].

Immunotherapy in the Cisplatin-Ineligible First-Line Setting

For patients with aUC who are ineligible for cisplatin-based chemotherapy in the frontline setting, the outcomes with carboplatin-based regimens are often inferior as opposed to cisplatin. This has led to the investigation of immunotherapy agents in this setting. Pembrolizumab in the frontline cisplatin-ineligible setting was investigated in the phase II KEYNOTE-052 trial (NCT02335424). This was a multicenter, single-arm trial of treatment-naïve patients with aUC who were cisplatin-ineligible [48•]. A total of 370 patients were treated with pembrolizumab 200 mg IV every 3 weeks for a total duration of 2 years or until confirmed progression or intolerable toxicity. The primary endpoint was ORR in all patients and according to PD-L1 expression status. Patients in this trial were cisplatin-ineligible due to estimated creatinine clearance < 60 ml/min (50%), followed by ECOG PS 2 (32%), both of these factors (9%), and other (9%). The patient population in this trial was perhaps representative of real world aUC population since the median age of patients was 74 with 29% of patients ≥ 80 years old and 42% with ECOG PS 2. Longer follow-up of this trial was presented at the 2017 ASCO Meeting. After a median follow-up of 5 months, ORR was 29% including 7% CR rate. A total of 58% of patients experienced a decrease in target lesions. At the time of data cutoff, 67% of responses were still ongoing. In a biomarker analysis, positive association with response was seen for PD-L1 combined positive score (CPS) and 18-gene expression profile (GEP) [49]. Among 110 patients with CPS ≥ 10, ORR was 38%. Grade ≥ 3 TRAEs occurred in 18% of patients. In May 2017, in addition to being granted regular approval in the platinum-refractory setting, pembrolizumab was also granted accelerated approval for patients with aUC who are cisplatin-ineligible in the first-line setting [35]. KEYNOTE-361, a phase III trial of pembrolizumab where treatment-naïve aUC patients in the frontline setting are randomized to pembrolizumab monotherapy, pembrolizumab and chemotherapy, or chemotherapy alone is currently ongoing with a goal to enroll almost 1000 patients (NCT02853305) [50].

As mentioned above, Cohort 1 of IMvigor 210 trial assessed the efficacy and safety of atezolizumab in the frontline setting for aUC patients who were cisplatin-ineligible. This was a single-arm multi-center trial which included 119 patients treated with atezolizumab 1200 mg IV every 3 weeks until progression [51•]. Primary endpoint of ORR was assessed in PD-L1 expression subgroups (IC0/1/2/3) as specified above. Included patients were cisplatin-ineligible based on creatinine clearance estimate < 60 ml/min, ECOG PS 2, or grade ≥ 2 hearing loss or neuropathy. After median follow-up of 17.2 months, ORR was 23% including 9% CR rate. Responses were durable as median response duration was not reached and occurred across all PD-L1 expression subgroups. Median PFS was 2.7 months and median OS 15.9 months. This compared favorably with historical OS data with frontline carboplatin-based regimens for cisplatin-ineligible patients with aUC (around 9 months); however, the IMvigor130 clinical trial in the first-line setting is ongoing [15]. Responses were also reported in challenging patient populations, such as patients with upper tract disease and patients over the age of 80. Similar to cohort 2, tumor mutation load was associated with response. Grade 3/4 TRAEs were reported in 16% of patients. Based on the data, in April 2017, the FDA granted atezolizumab accelerated approval as first-line treatment of aUC patients who are ineligible for cisplatin-based chemotherapy [52].

Choosing Among ICIs and Enhancing Immunotherapy Responses

After many years of very limited treatment options for patients with aUC refractory to platinum-based chemotherapy, there are now five different immunotherapy agents approved in this setting. This includes two anti-PD-1 agents (pembrolizumab, nivolumab) and three anti-PD-L1 agents (atezolizumab, avelumab, durvalumab). Choosing an ICI is probably largely based on efficacy, safety, level of evidence, treatment interval, patient convenience, available guidelines, local care paths, insurance coverage, and cost. The efficacy and safety profiles of these agents as summarized in Table 1 appear very comparable; however, inter-trial comparison should ideally be avoided. Pembrolizumab is the only agent currently supported by level I evidence with phase III trial data showing OS advantage compared to cytotoxic chemotherapy in platinum-refractory aUC. A similarly designed phase III trial of atezolizumab vs chemotherapy failed to meet its primary efficacy endpoint of OS in the IC 2/3 patient subset; however, there was OS difference favoring atezolizumab in the exploratory analysis of the entire study population. Four agents have received accelerated FDA approval based on phase I/II trials data. Consequently, pembrolizumab is considered the preferred standard of care for aUC patients who progressed on/after prior platinum-based chemotherapy, with atezolizumab, nivolumab, durvalumab, and avelumab being other standard options in this setting. For patients with aUC who are treatment-naïve but ineligible for cisplatin, both pembrolizumab and atezolizumab have shown robust anti-tumor activity and a favorable toxicity profile in single-arm phase II trials (Table 2). The data for atezolizumab from IMvigor 210 cohort 1 trial is a little more mature than the KEYNOTE-052 trial data, with reported median OS in that trial cohort fairly comparable with historical OS data from trials with cisplatin-based chemotherapy in this setting. However, there are some differences, e.g., in the baseline prognostic factors, sample size and follow-up time between the 2 ICI trials, while head to head comparison has not been performed; therefore, either ICI is very reasonable in cisplatin-ineligible patients as first-line therapy, especially in those who cannot tolerate chemotherapy. It is also worth noting that the optimal sequence or combination of chemotherapy and immunotherapy is not yet defined in aUC, and the ongoing clinical trials (both in first-line and maintenance settings) as well as retrospective registry studies will help answer such questions. For patients who received both platinum-based chemotherapy and immunotherapy, clinical trial is the preferred option; otherwise, chemotherapy with single-agent taxane (USA), vinflunine (European Union), or other agents with relatively limited data can be used.

Despite the promise shown by ICIs in aUC only a minority of patients have durable responses and the key questions in the years to come will focus on enhancing and optimizing responses to immunotherapy and properly utilizing the growing armamentarium of agents. While there is evidence of chemotherapy efficacy in patients previously treated with IOs [53], it is unknown whether treating patients with chemotherapy and immunotherapy combination upfront will produce deeper and more durable responses (tested in clinical trials). Combination therapies with other ICIs, chemotherapy, radiation, targeted, and anti-angiogenic therapies are being tested in clinical trials. For example, combining PD-1/PD-L1 agents with other immunotherapy agents holds significant promise. Combinations of pembrolizumab and epacadostat (IDO1 inhibitor), as well as nivolumab with ipilimumab (anti-CTLA-4 antibody), have shown robust anti-tumor activity and are being investigated further [54, 55].

Moreover, identification of patients most likely to benefit from ICIs and/or other treatments will be an important step towards the individualization of treatment patterns, based on tumor and host characteristics, as our understanding of the underlying disease and host biology improves. PD-L1 protein expression has thus far been clearly a suboptimal predictive biomarker of response to ICI. The association of treatment response with mutation load, molecular tumor subtypes, and gene expression signatures hold promise and need further

Table 1 Immune checkpoint inhibitors in the platinum-refractory setting

	Atezolizumab	Pembrolizumab	Nivolumab	Durvalumab	Avelumab
Trial phase	Phase II single arm	Phase III randomized trial	Phase II single arm	Phase I/II	Phase Ib
Number of patients	310	270	265	191	161 (> 6-month follow-up)
Dosing	1200 mg IV every 3 weeks	200 mg IV every 3 weeks	3 mg/kg IV every 2 weeks	10 mg/kg IV every 2 weeks	10 mg/kg IV every 2 weeks
ORR	15% (5% CR)	21.1% (7% CR)	19.6% (2% CR)	17.8% (3.7% CR)	17.4% (6.2% CR)
ORR among high PD-L1 expressors	26% (among IC2/3)	21.6% (among CPS ≥ 10)	28.4% (among PD-L1 ≥ 5%)	27.6% (among PD-L1 ≥ 25%)	25.4% (among PD-L1 ≥ 5%)
Median PFS	2.1 months	2.1 months	2.0 months	1.5 months	1.5 months
Median OS	7.9 months	10.3 months	8.7 months	18.2 months	7.4 months
Grade 3/4 TRAEs	16%	13.5% (15% for G3–5)	18%	6.8%	8.0% (8.4% for G3–5)

validation [26•, 27, 37•, 48•, 49, 51•, 56]. Additional preliminary data has implicated the importance of DNA damage response (DDR) and mismatch repair (MMR) gene mutations in predicting sensitivity to ICI, as well as the potential utility of next-generation sequencing of tumor tissue and cell-free circulating tumor DNA assessments to identify potential new treatment targets and biomarkers in aUC [57–61]. Evaluation of host factors, e.g., T cell clonality and diversity among others, has also been investigated with promising data that require further external validation [62].

Table 2 Immune checkpoint inhibitors in frontline cisplatin-ineligible setting

	Atezolizumab	Pembrolizumab
Trial phase	Phase II single arm	Phase II single arm
Number of patients	119	370
Dosing	1200 mg IV every 3 weeks	200 mg IV every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
ORR among high PD-L1 expressors	28% (among IC2/3)	38% (among CPS ≥ 10)
Median PFS	2.7 months	2 months
Median OS	15.9 months	Not reached
Grade 3/4 TRAEs	16%	18%

Conclusions and Future Directions

The past few years have seen significant advances in the treatment of aUC, mainly through the development of ICIs. In May 2016, atezolizumab received accelerated FDA approval for platinum-refractory aUC patients. Just a year later, pembrolizumab became the first ICI to show OS advantage compared to cytotoxic chemotherapy in the platinum-refractory setting, becoming the current standard of care in this setting. Nivolumab, avelumab, and durvalumab also have very promising efficacy in the platinum-refractory setting leading to their accelerated FDA approvals. The improved toxicity profile of ICIs relative to cytotoxic chemotherapy allows a number of aUC patients to be treated with these agents, including elderly and patients with compromised PS and medical comorbidities [63, 64]. In the frontline cisplatin-ineligible setting, both pembrolizumab and atezolizumab have demonstrated efficacy and very reasonable safety profile in large single-arm phase II clinical trials. A substantial proportion of aUC patients benefit from ICIs with ORR of 15–21% in the platinum-refractory setting and 23–29% in the frontline cisplatin-ineligible setting with a number of notable durable responses. However, as these numbers clearly point out, most patients do not respond to ICIs and much work remains to be done. Key questions include identifying patients most likely to respond to ICI, optimal sequencing of ICIs with chemotherapy and identifying novel combinations of immunotherapy and other agents that may produce deep and durable responses.

Recently reported and ongoing clinical trials are addressing many of these questions and remain very important treatment options for aUC patients in all (even earlier) disease and treatment settings [61]. There are also an increasing number of clinical trials that are evaluating "precision or personalized medicine" approaches targeted to the "molecular makeup" of the tumor based on biomarkers, regardless of the organ of tumor origin. Such trials may be either "umbrella type," which assess the utility of biomarkers and therapies in the same tumor type, or "basket type" that evaluate biomarkers and therapies across several tumor types. In the era of "molecular-based medicine," further understanding of tumor and host underpinnings can improve the use of immunotherapy via biomarker-based patient selection. However, until biomarkers are fully validated with proven clinical utility for patient selection, their use in immunotherapy in aUC remains currently investigational.

Compliance with Ethical Standards

Conflict of Interest Vadim S. Koshkin declares that he has no conflict of interest.

Petros Grivas has received compensation from Genentech, Dendreon, Bayer, Merck, Bristol-Myers Squibb, Exelixis, AstraZeneca, Biocept, Clovis Oncology, and EMD Serono for service as a consultant; participated in educational, unbranded, *not* product-related speaker's program (after providing direct input for slides content) for Genentech and Bristol-Myers Squibb; and received support for conduction of clinical trials (to Cleveland Clinic Foundation) from Genentech, Bayer, Merck, Mirati, Oncogenex, Pfizer, Bristol-Myers Squibb, and AstraZeneca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Cancer of the Urinary Bladder - Cancer Stat Facts. Available at: https://seer.cancer.gov/statfacts/html/urinb.html. Accessed: 15th November 2017.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
3. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol. 2003;44:672–81.
4. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48:202–5; discussion 205-206.
5. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23:4602–8.
6. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. Treatment of patients with metastatic urothelial cancer 'unfit' for cisplatin-based chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29:2432–8.
7. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol. 1988;139:461–9.
8. Loehrer PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol Off J Am Soc Clin Oncol. 1992;10:1066–73.
9. Sternberg CN, de Mulder PH, Schornagel JH, Théodore C, Fossa SD, van Oosterom A, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol Off J Am Soc Clin Oncol. 2001;19:2638–46.
10. Sternberg CN, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer Oxf Engl. 2006;1990(42):50–4.
11. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol Off J Am Soc Clin Oncol. 2000;18:3068–77.
12. Bamias A, Dafni U, Karadimou A, Timotheadou E, Aravantinos G, Psyrri A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol. 2013;24:1011–7.
13. Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol. 2012;23:406–10.
14. De Santis M, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer 'unfit' for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:5634–9.
15. De Santis M, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30:191–9.
16. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24:3451–7.
17. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2002;20:937–40.
18. Lorusso V, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer Oxf Engl. 1998;1990(34):1208–12.
19. McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI, et al. Phase II trial of docetaxel in patients with advanced or

metastatic transitional-cell carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 1997;15:1853–7.
20. Witte RS, Elson P, Bono B, Knop R, Richardson RR, Dreicer R, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 1997;15:589–93.
21. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:4454–61.
22. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med. 2016;375:1767–78.
23. Brown JA, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol Baltim Md. 2003;1950(170):1257–66.
24. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515:558–62.
25. Petrylak DP, Powles T, Bellmunt J, Braiteh FS, Loriot Y, Morales R, et al. Atezolizumab (atezo) in patients with metastatic urothelial carcinoma (mUC): a 2-year clinical update from a phase Ia study. J Clin Oncol. 2017;35:290.
26.• Rosenberg JE, 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. **Summarizes the results of Cohort 2 in IMvigor 210, a phase II trial of atezolizumab in platinum-refractory aUC. This trial led to the first approval of an immunotherapy agent (atezolizumab) in platinum-refractory aUC.**
27. Rosenberg JE, et al. PD-L1 expression, cancer genome atlas (TCGA) subtype, and mutational load as independent predictors of response to atezolizumab (atezo) in metastatic urothelial carcinoma (mUC; IMvigor210). J Clin Oncol. 2016;34:104.
28. Necchi A, et al. Atezolizumab (atezo) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC): post-progression outcomes from the phase 2 IMvigor210 study. Ann Oncol. 2017;28(suppl_5):v295–329. https://doi.org/10.1093/annonc/mdx371.
29. Press Announcements - FDA approves new, targeted treatment for bladder cancer. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm. Accessed: 18th November 2017.
30. A study of atezolizumab compared with chemotherapy in participants with locally advanced or metastatic urothelial bladder cancer [IMvigor211]—full text view - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02302807. Accessed: 17th November 2017.
31. Roche provides update on phase III study of TECENTRIQ® (atezolizumab) in people with previously treated advanced bladder cancer. Available at: http://www.roche.com/media/store/releases/med-cor-2017-05-10.htm. Accessed: 18th November 2017.
32. Powles, 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. 2017.
33. Plimack ER, Bellmunt J, Gupta S, Berger R, Chow LQM, Juco J, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol. 2017;18:212–20.
34.•• Bellmunt J, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376:1015–26. **Summarizes the results of a landmark phase III trial (KEYNOTE-045) showing an overall survival advantage of pembrolizumab compared to chemotherapy in platinum-refractory aUC. This trial established pembrolizumab as the current standard of care in platinum-refractory aUC.**
35. Research, C. for D. E and. approved drugs—pembrolizumab (Keytruda): advanced or metastatic urothelial carcinoma. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm559300.htm. Accessed: 18th November 2017.
36. Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol. 2016;17:1590–8.
37.• Sharma P, 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. **Summarizes results of CheckMate 275, a phase II trial of nivolumab in platinum-refractory aUC.**
38. Research, C. for D. E. and approved drugs - Nivolumab for Treatment of Urothelial Carcinoma. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm539646.htm. Accessed: 18th November 2017.
39. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34:3119–25.
40.• Hahn NM, et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma (UC). J Clin Oncol. 2017;35:4525. **Abstract with the most updated results of the trial of durvalumab in platinum-refractory aUC. The Massard et al. reference above describes in manuscript form an earlier analysis of the same trial.**
41. Research, C. for D. E. and approved drugs—durvalumab (Imfinzi). Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm555930.htm. Accessed: 18th November 2017.
42. Study of MEDI4736 with or without tremelimumab versus standard of care chemotherapy in urothelial cancer—full text view - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02516241. Accessed: 18th November 2017.
43. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN solid tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol. 2017;18:587–98.
44. Apolo AB, Infante JR, Balmanoukian A, Patel MR, Wang D, Kelly K, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:2117–24.
45. Patel MR, Ellerton JA, Infante JR, Agrawal M, Gordon MS, Aljumaliy R, et al. Avelumab in patients with metastatic urothelial carcinoma: pooled results from two cohorts of the phase 1b JAVELIN solid tumor trial. J Clin Oncol. 2017;35:330.
46.• Apolo AB, et al. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. J Clin Oncol. 2017;35:4528. **Abstract describing the most updated results of the phase Ib trial of avelumab in platinum-refractory aUC patients.**
47. Research, C. for D. E. and. Approved drugs—FDA grants accelerated approval to avelumab for urothelial carcinoma. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm557162.htm. Accessed: 18th November 2017.
48.• Balar AV, 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; https://doi.org/10.1016/S1470-2045(17)30616-2. **Summarizes the results of KEYNOTE-052, a phase II study of pembrolizumab in cisplatin-ineligible aUC.**

49. O'Donnell PH, Grivas P, Balar AV, Bellmunt J. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). ASCO; 2017.
50. Powles T, et al. Phase 3 KEYNOTE-361 trial: pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer. J Clin Oncol. 2017;35:TPS4590.
51.• Balar AV, 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. **Summarizes the results of Cohort 1 in IMvigor 210, a phase II trial of atezolizumab in cisplatin-ineligible patients.**
52. FDA grants Roche's TECENTRIQ® (atezolizumab) accelerated approval as initial treatment for certain people with advanced bladder cancer. Available at: http://www.roche.com/media/store/releases/med-cor-2017-04-18.htm. Accessed: 19th November 2017.
53. Szabados B, Van Der Heijden MS, Gomez De Liano Lista A, Tang YZ, Powles T. Responses to chemotherapy in patients with metastatic urothelial cancer (MUC) after frontline immunotherapy. J Clin Oncol. 2017;35:–e16004.
54. Sharma P, Callahan MK, Calvo E. Efficacy and safety of nivolumab plus ipilimumab in previously treated metastatic urothelial carcinoma: first results from the phase I/II CheckMate 032 study. In: 2016 SITC Annual Meeting; 2016.
55. Smith DC, et al. Epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma: preliminary phase I/II results of ECHO-202/KEYNOTE-037. J Clin Oncol. 2017;35:–4503.
56. Robertson AG, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell. 2017;171:540–556.e25.
57. Iyer G, et al. Mismatch repair (MMR) detection in urothelial carcinoma (UC) and correlation with immune checkpoint blockade (ICB) response. J Clin Oncol. 2017;35(15_suppl):4511.
58. Teo M, et al. DNA damage repair and response (DDR) gene alterations (alt) and response to PD1/PDs1 blockade in platinum-treated metastatic urothelial carcinoma (mUC). J Clin Oncol. 2017;35:4509.
59. Le DT, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409–13.
60. Barata PC, Koshkin VS, Funchain P, Sohal D, Pritchard A, Klek S, et al. Next-generation sequencing (NGS) of cell-free circulating tumor DNA and tumor tissue in patients with advanced urothelial cancer: a pilot assessment of concordance. Ann Oncol. 2017;28:2458–63.
61. Galsky MD, Wang H, Hahn NM, Twardowski P, Pal SK, Albany C, et al. Phase 2 trial of gemcitabine, cisplatin, plus ipilimumab in patients with metastatic urothelial cancer and impact of DNA damage response gene mutations on outcomes. Eur Urol. 2017.
62. Funt S, et al. Correlation of peripheral and intratumoral T-cell receptor (TCR) clonality with clinical outcomes in patients with metastatic urothelial cancer (mUC) treated with atezolizumab. J Clin Oncol. 2016;34(15_suppl):3005.
63. Grivas P, et al. Pembrolizumab (pembro) as first-line therapy in cisplatin-ineligible advanced urothelial cancer (UC): outcomes from KEYNOTE-052 in senior patients (pts) with poor performance status. Ann Oncol. 2017;28(suppl_5):v295–329.
64. Powles T, et al. Immune checkpoint inhibition in metastatic urothelial cancer. Eur Urol. 2017;72(4):477–81.