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Immunotherapy and urothelial carcinoma: An overview and future prospectives

Francesco Pierantoni[a,*], Marco Maruzzo[a], Mario Gardi[b], Elisabetta Bezzon[c], Marina Paola Gardiman[d], Angelo Porreca[e], Umberto Basso[a], Vittorina Zagonel[a]

[a] Medical Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto IOV IRCSS, Padua, Italy
[b] Urology Unit, Department of Surgery, Sant'Antonio Hospital, Padua, Italy
[c] Radiology Unit, Department of Imaging and Medical Physics, Istituto Oncologico Veneto IOV IRCSS, Padua, Italy
[d] Surgical Pathology and Cytopathology Unit, Department of Medicine, University Hospital of Padua, Italy
[e] Urology Unit, Policlinico Abano Terme, Abano Terme, Italy

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ABSTRACT

Background: Urothelial carcinoma (UC) is a common malignancy with a high mortality rate when metastatic. Traditionally, systemic therapy consisted in platinum-based regimens as first-line, with Taxanes or Vinflunine as further lines. Recently, checkpoint inhibitors (CPIs) immunotherapy has emerged as a new therapeutic option.
Methods: We searched in Medline, Pubmed and ClinicalTrial.gov databases for the relevant literature, reviewing the results of published trials and the design of ongoing studies involving CPIs in UC.
Result: Strong evidence supports the use of CPIs after failure of Cisplatin-based chemotherapy, although no predictive parameter is available so far. Expression of Programmed-Death-1-Ligand has given conflicting results, and is currently indicated only for the selection of Cisplatin-ineligible patients who should receive CPIs.
Conclusion: The therapeutic landscape of UC is rapidly changing due to the availability of CPIs. Neoadjuvant trials with CPIs and trials combining two CPIs are promising and will further expand the use of immunotherapy.

1. Introduction

Bladder and upper urinary tract cancers are quite common malignancies, accounting for 4% of all cancers in the European population, with an age-standardized incidence of 12.4–21.8 per 100.000 males-years and 2.7–4.3 per 100.000 women-years in different parts of Europe (Antoni et al., 2017). The predominant histology is urothelial carcinoma (UC) with a minority of tumors showing squamous, plasmacytoid and sarcomatoid differentiation. Approximately one fourth of patients with bladder cancer have muscle-invasive disease (pT2 or more according to TNM staging) which requires a combined approach of neoadjuvant chemotherapy and radical surgery, with an emerging role of chemo-radiotherapy combination in selected cases (Chang et al., 2017). Worldwide age-standardized mortality rate is 3.2 per 100.000 males-years and 0.9 per 100.000 women-years, as metastatic recurrences are frequent and almost invariably incurable (Witjes et al., 2017).

UC has long been known to be responsive to immunological strategies since topical therapy with Bacillus of Calmette-Guérin (BCG) has consistently shown to reduce relapses of high risk, non muscle-invasive disease in several studies (Patard et al., 2002). UC appeared therefore a good candidate for experimenting more innovative forms of immunotherapy such as the new checkpoint inhibitors (CPIs) which have revolutionized the treatment of advanced melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).

Tumor cells can suppress the activity of the immune system by overproducing immunosuppressive factors or by exposing on their surface ligands which inhibit the lymphocytes, activating the programmed-death receptor 1 (PD-1) and cytotoxic-T-lymphocyte-associated protein 4 (CTLA-4). These molecules are widely known as "immune checkpoints" (Vinay et al., 2015; Li et al., 2018).

CPIs are monoclonal antibodies (mAbs) specifically developed to target the aforementioned inhibitory pathways of the immune system. Many different CPIs have been produced and tested in clinical trials: Nivolumab and Pembrolizumab bind directly to PD-1, Avelumab, Atezolizumab and Durvalumab bind to programmed death 1 ligand (PD-L1), while Ipilimumab and Tremelimumab bind to CTLA-4. Interaction between CPIs and their corresponding immune checkpoints results in an increase of local and systemic immune response against tumor cells.

* Corresponding author at: Medical Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto IOV IRCCS, Via Gattamelata 64, 35128 Padova, Italy.
E-mail address: francesco.pierantoni@iov.veneto.it (F. Pierantoni).

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Unfortunately, tumors are not equally sensitive to immune response. For instance, immunotherapy seems to work better on neoplasms with an elevated mutational burden, which probably translates into a major quantity of potential tumor-specific antigens recognized by the adaptive immune response. Similarly to melanoma and NSCLC, UC not only displays a high mutational burden (Alexandrov et al., 2013) but it also expresses relatively high levels of PD-L1 (Bellmunt et al., 2015), which has shown a strong correlation with efficacy of CPIs in lung cancer (Garon et al., 2015).

Thus, new therapeutic strategies with CPIs have been and are being progressively explored in UC, at first in the metastatic disease, and then also in the neoadjuvant and adjuvant settings.

The traditional treatment for metastatic UC has long been systemic chemotherapy, predominantly platinum-based regimens comprehensive of Cisplatin plus Gemcitabine (CG), or Cisplatin plus Methothrexate, Doxorubicin and Vinblastine (MVAC). These two regimens achieved similar Overall Survival (OS) rates of around 14 months in a large, randomized phase 3 study, with a hazard ratio (HR) of 1.04 a (95% confidence interval - CI of 0.82–1.32; p = 0.75). In the same way, time to treatment failure (HR = 0.89; 95% CI, 0.72–1.10; p = 0.27) and overall response rate (49% for GC and 46% for MVAC; p = 0.51) were not significantly different. However, GC is frequently preferred due to its lower hematological (2% febrile neutropenia for GC vs 14% for MVAC) and mucosal toxicity (Von der Maase et al., 2000). Patients unfit for Cisplatin were usually treated with Carboplatin plus Gemcitabine which showed ORR of 41.2% and a median OS of 9.3 months (De Santis et al., 2012). Until a few years ago standard second line treatments included Taxanes (Docetaxel or Paclitaxel) or Vinflunine (which is approved and available only in Europe and some other countries. Vinflunine showed an Objective Response Rate (ORR) of 8% and a modest clinical benefit over best supportive care (BSC) in a phase 3 trial (median OS 6.9 vs 4.3 months; HR = 0.77; 95% CI, 0.61 to 0.98; p = 0.036) (Bellmunt et al., 2009), while Docetaxel and Paclitaxel achieved an ORR of 13.3% and 10%, respectively, in phase 2 trials (McCaffrey et al., 1997; Vaughn et al., 2002), but their impact on OS has never been demonstrated.

Given the disappointing scenario, results of phase 1 and 2 studies with CPIs were deemed sufficiently promising to grant formal approval by Regulatory Agencies in a short time after the first responses were described in metastatic UC. In fact, from 2017 to now, up to five different mAbs targeting checkpoints of the immune system have been approved by the Food and Drug Administration (FDA) for UC: Atezolizumab, Pembrolizumab, Nivolumab, Durvalumab and Avelumab. Yet, only Pembrolizumab showed a significant increase in OS vs standard second line chemotherapy in a randomized, phase 3 trial (KEYNOTE-045). Atezolizumab was approved on the basis of a positive single-arm phase 2 trial (IMVIGOR-210), but the phase 3 trial IMVIGOR-211 failed to demonstrate better OS outcomes compared to chemotherapy. Nivolumab, Durvalumab and Avelumab still lacks OS data in randomized, phase 3 trials.

Nowadays the most important international guidelines include CPIs as the best choice for second line treatment after progression to Cisplatin-based chemotherapy (Flaig et al., 2018). However, it is important to underline that not all the drugs mentioned have been approved by the European Medicines Agency (EMA), and in some European countries none of them is reimbursed.

In this paper we review the results of most relevant clinical trials conducted with CPIs in UC patients with metastatic disease or treated in the adjuvant and neoadjuvant settings. Then, we discuss the most relevant challenges in the use of CPIs in UC and we briefly summarize the ongoing trials in metastatic or localized muscle-invasive disease. We performed an electronic, systematic search in Medline, Pubmed© databases, using the terms “urothelial carcinoma”, "bladder cancer", "urinary tract cancer", “immunotherapy”, “checkpoint inhibitors”, “Atezolizumab”, “Pembrolizumab”, “Nivolumab”, “Durvalumab”, “Avelumab”, "Ipilimumab", "Tremelimumab", "metastatic", "adjuvant", "neoadjuvant". Moreover, we searched all active trials on ClinicalTrial.gov, using the same terms. Original articles and reviews were selected on the basis of their clinical and scientific relevance. References from the selected papers were then examined to find out any possible interesting article missing from our initial search.

2. Metastatic disease

2.1. Immunotherapy in the post-platinum setting

Atezolizumab is an IgG monoclonal antibody targeting PD-L1. After small phase I studies, a two arms, phase II trial (IMVIGOR-210) was planned in order to assess the activity of intravenous Atezolizumab, flat dose of 1200 mg every three weeks, in two cohorts of patients. The first cohort consisted of 119 patients affected by locally advanced or metastatic UC who were Cisplatin-ineligible and received Atezolizumab as a first systemic regimen (see below). The second cohort enrolled 315 patients who had progressed after a first platinum-based regimen. In this cohort, objective response rate (ORR) was 15% with a long duration of response (84% of the responders were still progression-free after 11.7 months of median follow-up). Patients’ tumor samples from cystectomy or biopsies were collected, and PD-L1 expression was assessed centrally with immunohistochemistry (IHC, VENTANA assay). The PD-L1 tumor-infiltrating immune cell (IC) status was defined by the ratio of PD-L1 positive immune cells observed in the tumor microenvironment, thus dividing the tumors in three categories: IC0 (< 1%), IC1 (≥1% but < 5%) and IC2/3 (≥5%). A pre-planned subgroup analysis showed that patients with an elevated PD-L1 expression (IC2/3) had a higher ORR (26%) compared to those with a lower PD-L1 staining (18%). Median OS in the IC2/3 group was 11.4 months, vs 6.7 of the IC1 and 6.5 of the IC0 group. Progression Free Survival (PFS) according to response evaluation criteria in solid tumors 1.1 (RECIST 1.1) was 2.1 months for all patients, and it was very similar in all the groups (2.1 months for IC2/3 and IC 1/2/3). Grade 3–4 treatment related AEs were present in 5% of patients and consisted mainly of pneumonitis, increased transaminases and rash (Rosenberg et al., 2016). The results of this study led to the approval by FDA (May 2016) and then by EMA (September 2017) of Atezolizumab as a second line treatment for relapsing patients after platinum-based chemotherapy.

Meanwhile, a confirmatory phase 3 randomized, open-label protocol comparing Atezolizumab to standard chemotherapy (Taxanes or Vinflunine) as a second line regimen has been completed (IMVIGOR-211). Patients were stratified according to central PD-L1 immunohistochemistry staining on immune cells as in the IMVIGOR-210 trial. The primary endpoint was OS, secondary endpoints were investigator-assessed ORR, PFS, duration of response. OS was planned to be tested in a hierarchically fixed sequence of prespecified populations: IC2/3, IC1/2/3, and intention to treat (ITT). From 198 sites, 931 patients were enrolled in the study: 467 received Atezolizumab, while 464 received chemotherapy. Surprisingly, no significant improvement in OS was observed in the IC2/3 group which achieved a median OS of 11.1 months with Atezolizumab vs 10.6 months with chemotherapy (HR = 0.87; 95% CI, 0.63–1.21; p = 0.41). The negative results in the IC2/3 population precluded further statistical comparisons, although Atezolizumab improved OS in the ITT population compared to chemotherapy (medians: 8.6 vs 8.0 months; HR = 0.85; 95% CI, 0.73 to 0.99). Interestingly, Atezolizumab reached higher OS compared to Taxane arm (median: 8.3 months vs 7.5 months; HR = 0.73; 95% CI, 0.58 to 0.92), but not compared to Vinflunine arm, which performed better compared to historical cohorts treated with this drug (medians: 9.2 months vs 8.3 months; HR = 0.97; 95% CI, 0.78–1.19). No significant differences were found also in terms of PFS (median of 2.4 months with Atezolizumab vs 4.2 months with chemotherapy; HR = 1.1; 95% CI, 0.75–1.34), and ORR (22% vs 23%, respectively). However, Atezolizumab showed improved duration of response with a median of 15.9 months vs 8.3 months with chemotherapy (HR = 0.57;

95% CI, 0.26–1.26). Toxicity profile was in favor of immunotherapy group with 20% of grade 3–4 AEs vs 43% in the chemotherapy group; the toxicity profile of immunotherapy appeared superimposable to previous studies with Atezolizumab (Powles et al., 2018a).

Pembrolizumab is a humanized IgG4 mAb targeting PD1, widely known for its remarkable results in the treatment of melanoma and NSCLC. The efficacy of Pembrolizumab in UC was established by the KEYNOTE-045 study, a phase 3, open-label randomized trial enrolling 542 patients. Eligible individuals had to have progressed after a platinum-based regimen, and were randomized to receive Pembrolizumab monotherapy (200 mg every three weeks) or chemotherapy by investigators' choice (Paclitaxel, Docetaxel or Vinflunine). Primary endpoints were OS and PFS in overall population and in the PD-L1 positive subgroup. PD-L1 was assessed by IHC (DAKO assay) on tumor tissue samples, and positivity was defined as having a Combined Positive Score (CPS) > 10%, calculated as the ratio between the sum of cancer cells and infiltrating immune cells expressing PD-L1 divided by the total number of cancer cells. Median OS was significantly longer in the Pembrolizumab arm compared to chemotherapy in the whole population (10.3 months vs 7.4 months; HR = 0.73; 95% CI, 0.59 to 0.91; p = 0.002), as well as in the PD-L1 positive subgroup (10.3 months vs 7.4 months; HR = 0.73; 95% CI, 0.59 to 0.91; p = 0.002). Median PFS was 2.1 months in the Pembrolizumab group and 3.3 months in the chemotherapy group (HR = 0.98; 95% CI, 0.81–1.19; p = 0.42), with no significant difference achieved also in the PD-L1 positive group (HR = 0.89; 95% CI, 0.61–1.28; p = 0.24). Less toxicity was observed in the immunotherapy arm: 15.0% grade 3–4 treatment related AEs (most frequently fatigue and diarrhea) vs 49.4% in the chemotherapy group (Bellmunt et al., 2017). On the basis of these results, Pembrolizumab was approved by FDA on May 2017, and by EMA on September 2017.

Durvalumab is an anti-PD-L1 human IgG1. In the 1108 study, 191 patients affected by advanced UC and progressing after or ineligible for platinum-based chemotherapy, received Durvalumab 10 mg/kg every two weeks. Patients were enrolled regardless of PD-L1 status but were divided according to positive or negative PD-L1 expression. In this study PD-L1 was evaluated with IHC on tumor tissue (VENTANA assay) and positivity was defined as > 25% of tumor and infiltrating immune cells expressing PD-L1.

As a phase 1/2 study, the primary endpoint was safety; secondary endpoints were ORR, disease control rate at 12 weeks, OS and PFS. An ORR of 17.8% was reported but RR was 27.6% in the PD-L1 positive subgroup and 5.1% in the PD-L1 negative subgroup. Disease control rate at 12 weeks was 57.1% in the PD-L1 positive subgroup and 28.6% in the PD-L1 negative subgroup. Median PFS and OS were 1.5 months and 18.2 months, respectively. Severe toxicities were rare (6.8% of Grade 3–4 AEs, consisting mainly in increased transaminases), but there were 2 deaths due to autoimmune hepatitis and pneumonitis, respectively (Powles et al., 2017). These promising results lead to registration of Durvalumab by FDA on May 2017.

Nivolumab is a human IgG mAb targeting PD1. It was first studied as monotherapy in advanced UC patients in the phase 1/2 open-label study CHECKMATE-032. The primary endpoint was ORR with safety, PFS and OS as secondary end-points. The study enrolled 78 patients, 65.4% of whom had received two or more previous lines of chemotherapy. Tumor response was observed in 19 (24.4%) patients. Grade 3–4 AEs occurred in the 20.5% of patients, the most frequent being increased lipase and amylase, fatigue and dyspnea (Sharma et al., 2016). These results were confirmed by the CHECKMATE-275, a phase 2 single-arm study which involved 265 patients with advanced UC, progressing after a platinum-based chemotherapy. Patients were treated with Nivolumab 3 mg/Kg every two weeks. The endpoint was ORR in all the study population and in the subpopulation of patient expressing PD-L1 levels ≥5% and ≥1% on tumor cells surface at IHC (DAKO assay). ORR was 19.6% in the ITT, 28.4% in the PD-L1 ≥ 5% group, 23.8% in the PD-L1 ≥ 1% and 16.1% even in the PD-L1 negative patients. In this study, 18% of the patients experienced grade 3–4 events (the most common being fatigue and diarrhea) and there were 3 toxic deaths (Sharma et al., 2017). The promising ORR results in all the subgroups led to Nivolumab registration by FDA on February 2017 and by EMA on June 2017.

Avelumab is a human IgG1 mAb against PD-L1. Two cohorts of the phase 1b trial JAVELIN enrolled 249 patients affected by advanced UC who had progressed after, or were ineligible for a first line, platinum-based, chemotherapy. The primary endpoint was safety, secondary endpoints were number, severity and duration of treatment-related AEs, pharmacokinetic e pharmacodynamic profiles and best overall response. Avelumab showed an acceptable toxicity profile up to 20 mg/kg, and 10 mg/kg every two weeks was the schedule chosen for subsequent trials. It has to be noted that the constant fragment (Fc) of Avelumab is unaltered, so it is able to activate antibody-dependent cell-mediated cytotoxicity, a feature unique to this particular drug; however, its half-life (3.4–4.1 days) is shorter compared to other CPIs. A partial or complete response was recorded in 17% of the patients, 47% of whom were alive and without progression of disease at 12 weeks. In the PD-L1 positive group, which was defined as having ≥ 5% of positive tumor cells by IHC (DAKO assay), ORR was 40% vs 9% in the PD-L1 negative group. About 8% of the patients had a G3–4 AEs, the most common being asthenia. There was one toxic death (Apolo et al., 2016; Heery et al., 2017). FDA approved Avelumab on the basis of these results on May 2017.

Table 1 summarizes the approval status of the five CPIs by FDA and EMA, with differences that are due to the designs of available trials and strength of scientific evidence. Up to date only Pembrolizumab has shown an increased OS in a phase 3 randomized trial compared to standard chemotherapy. Atezolizumab showed promising ORR in the phase 2 trial, but the phase 3 registration trial failed to demonstrate a solid increase in OS in the PD-L1 positive cohort, and this may lead to reimbursement issues in some countries (*e.g.* Italy). There could be many possible reasons why the IMVIGOR-211 was not able to achieve its primary endpoint. As addressed by the investigators, the IHC assay used could be part of the problem. Indeed, in this trial overexpression of PD-L1 in infiltrating immune cells (using the SP142 antibody – VENTANA assay) was actually associated with longer OS and ORR both with Atezolizumab or chemotherapy (Powles et al., 2018a). On the other hand, in the KEYNOTE-045 trial the expression of PD-L1 was assessed with a different assay (22C3 antibody – DAKO assay) and on both immune and tumor cells (CPS), and overexpression was associated with higher ORR in the arm treated with CPIs, as expected (Bellmunt et al., 2017).

In addition, most of the tumor samples collected for the IMVIGOR-211 were from archived paraffined tissue, which of course may not be

Table 1
.Current registration status of CPIs for the treatment of metastatic UC at FDA and EMA.

Drug	FDA approval	EMA approval	Trial	Type
Atezolizumab	18 May 2016	22 Sep 2017	IMVIGOR-210 (phase 2) (Rosenberg et al., 2016)	Anti-PD-L1
Nivolumab	02 Feb 2017	05 Jun 2017	CHECKMATE-275 (phase 2) (Sharma et al., 2017)	Anti-PD1
Durvalumab	01 May 2017	N/A	1108 Durvalumab (phase 1B) (Powles et al., 2017)	Anti-PD-L1
Avelumab	09 May 2017	N/A	JAVELIN (phase 1B) (Apolo et al., 2016)	Anti-PD-L1
Pembrolizumab	18 May 2017	05 Sep 2017	KEYNOTE-045 (phase 3) (Bellmunt et al., 2017)	Anti-PD1

representative of the tumor immune infiltration status in metastatic sites immediately before the beginning of immunotherapy with Atezolizumab.

Nivolumab, Avelumab and Durvalumab were approved on the basis of a phase 1 and/or 2 trials, whose primary endpoint was safety and/or ORR. All these drugs showed promising ORRs, but data about OS comparisons with standard treatments are not available.

A recent meta-analysis designed to compare the phase 3 pivotal studies of Atezolizumab and Pembrolizumab (with Vinflunine as control arm) concluded that at the moment Pembrolizumab seems to be the best choice for this particular setting of patients (Rassy et al., 2018). Although the median OS reached by Atezolizumab in the IMVIGOR-211 (Powles et al., 2018a) and by Pembrolizumab in the KEYNOTE-045 (Bellmunt et al., 2017) were comparable, Vinflunine performed better in the first than in the latter trial for reasons that are difficult to explain. While waiting for long term results and additional translational researches, Pembrolizumab is going to become the new standard of care for second line treatment of metastatic UC patients.

It is worthwhile to highlight the lack of a validated biomarker predictive of response. A considerable proportion of patients affected by UC do not benefit from CPIs or, paradoxically, may even experience an increase of the disease growth rate (a phenomenon known as hyperprogression, described in patients with melanoma or lung cancer) and there are not clinical parameters predictive of this detrimental effect (Champiat et al., 2017). Differently from NSCLC, in UC there is not a validated threshold of PD-L1 positivity predictive of response to Pembrolizumab, as well for Atezolizumab or all other CPIs. Indeed, PD-L1 level appears to correlate with ORR in the Durvalumab and Nivolumab studies, but did not correlate with primary endpoint of OS in the phase 3 Atezolizumab and Pembrolizumab trials. As previously described, assessment methods of this marker were heterogeneous. Not only different antibodies were used for the IHC assays (VENTANA or DAKO), but PD-L1 was assessed on immune cells only in the Atezolizumab case, in both tumor and immune cells in the Pembrolizumab and Durvalumab ones, and on tumor cells only in Nivolumab and Avelumab cases.

2.2. Immunotherapy in the first line setting in Cisplatin-ineligible patients

In consideration of their more favorable profile of toxicity, CPIs have been tested as first line monotherapy in patients who are ineligible for a Cisplatin-based chemotherapy. Cisplatin ineligibility is usually defined by one of more of the following conditions: glomerular filtration rate (GFR) < 60 mL/min, ECOG performance status of 2 (or Karnofsky performance status of 60–70%), G2 or higher peripheral neuropathy, $\geq$G2 hearing impairment or New York Heart Association (NYHA) heart failure class III-IV (Galsky et al., 2011a). Cisplatin-unfit patients usually account from 30 to 50% of the stage IV UC population, especially due to the high prevalence of renal impairment or lower performance status in the wide subgroup of older and/or heavy smoker patients (Galsky et al., 2011b).

Up to now, the preferred therapy in this setting was the combination of Carboplatin plus Gemcitabine (CarboGem), because Carboplatin has lower rates of renal and neurological toxicities compared to Cisplatin, and is more manageable in unfit patients. CarboGem performed slightly better compared to Methotrexate plus Carboplatin and Vinblastine (M-CAVI) in a phase II/III randomized trial in this specific category of patients. The ORR for CarboGem was 41.2%, median OS was 9.3 months (vs 8.1 with m-CAVI; HR = 0.94; 95% CI, 0.8–1.35; p = 0.64) and PFS was 5.8 (vs 4.2; HR = 1.04; 95% CI 0.8–1.35; p = 0.78) (De Santis et al., 2012).

The first cohort of patients of the IMVIGOR-210 study consisted of 119 chemo-naive, Cisplatin-ineligible patients, who received Atezolizumab monotherapy, 1200 mg every three weeks. Primary endpoint was ORR, with OS and PFS as secondary objectives. ORR was 23% (regardless of PD-L1 status) with 9% of complete responses (CR) and 12% of partial responses (PR). Median PFS was 2.7 months, while median OS was interestingly 15.9 months. Severe adverse events were registered in 12% of the patients, with one death potentially related to treatment (Balar et al., 2017a). Both OS and toxicity data compared favorably with historical data achieved by standard regimen of CarboGem in this setting of patients (De Santis et al., 2012), thus prompting FDA to grant accelerated approval for Atezolizumab also as first regimen for Cisplatin-ineligible patients.

The phase 2 KEYNOTE-052 trial enrolled 374 Cisplatin-ineligible subjects who were stratified for PD-L1 status and treated with Pembrolizumab 200 mg every three weeks. In all comers, ORR was 24%, while 53% of patients had progression as their best response. A cut-off of 10% CPS was the threshold for positivity (same as the previously described KEYNOTE-045 trial), and 38% of the 110 PD-L1 positive patients obtained an objective response. Sixteen percent of patients experienced a serious treatment-related adverse event, the most common being fatigue, colitis and muscle-weakness, one patient died from treatment-related autoimmune toxicity (Balar et al., 2017b). Both FDA and EMA approved Pembrolizumab for first-line treatment of Cisplatin-ineligible patients.

The favorable results of CPIs in the Cisplatin-ineligible populations, prompted to test CPI monotherapy also in Cisplatin-fit patients in two phase 3 randomized, placebo-controlled trials with Pembrolizumab and Atezolizumab (KEYNOTE-361 and IMVIGOR-130, respectively). In both trials there is a cohort of Cisplatin-fit patients treated with CPI monotherapy, along with two arms of patients treated with combination of chemotherapy plus CPI or placebo. However, in May 2018 FDA Data Monitoring Committee review found that patients with low PD-L1 expression in the CPI monotherapy arm had decreased survival compared to patients receiving Cisplatin or Carboplatin based chemotherapy. On the basis of those findings, first FDA and then EMA discouraged the administration of CPIs as first line regimen in PD-L1 negative patients, and both trials were consequently amended.

Although it is not possible to make statistically valid comparisons across studies conducted in different times and populations, results of these trials with first line CPIs may strongly influence clinical practice. With the ageing of population in developed countries, future patients with advanced UC will probably present with higher prevalence of comorbidities such as chronic renal and heart failure, making them unfit for Cisplatin. Nowadays the choice is between Carboplatin-based chemotherapy or a CPI (Pembrolizumab or Atezolizumab) which has the advantage of inducing less toxicities. CarboGem achieved in different studies a median OS of about 10 months, other chemotherapy regimens with Taxanes and Gemcitabine reached similar results (Necchi et al., 2017). The IMVIGOR-210 study showed a promising median OS of 15.9 months, which is probably related to the longer duration of disease control in responsive patients (Balar et al., 2017a). Obviously, additional and possibly randomized trials are needed to provide additional data defining the best treatment option for Cisplatin-unfit patients. For the time being, demonstration of expression of PD-L1 is required in order to propose a first-line CPI to these patients. In particular, for Atezolizumab it is requested a PD-L1 expression equal or greater than 5% of the immune cells in the tumor environment, and for Pembrolizumab a CPS equal or greater than 10%.

Considering the palliative objective of these therapies, toxicity is also a major concern. In the first line setting 12% of patients treated with Atezolizumab and 10% of the ones treated with Pembrolizumab experienced severe adverse events, and in the population of both studies there was one drug-related death (Balar et al., 2017a, b), while patients treated with CarboGem experienced a much higher rate of G3–4 toxicities, especially myelosuppression (44.9% leucopenia, 52.5% neutropenia, 48.3% thrombocytopenia) (De Santis et al., 2012).

Even in trials for other neoplasms first line immunotherapy showed lower toxicity rates: for example, in NSCLC Pembrolizumab induced 26.6% of G3–4 events vs 53.3% of standard chemotherapy (Reck et al., 2016). Furthermore, the randomized second-line trials conducted in UC confirmed that immunotherapy is better tolerated compared to

Table 2
Adjuvant studies with CPIs in urothelial carcinoma.

Intervention	Indication	Phase	Primary Endpoint	Trial ID
Nivolumab q4w for 1 year	Adjuvant after chemo-radiotherapy	Phase II	2-year failure-free survival	NCT03171025
Durvalumab q4w for 1 year	Concomitant with radical radiotherapy and adjuvant	Phase IB/II	Safety PFS at 1 year Disease control rate at 15 months	NCT02891161
Pembrolizumab 1 yr vs observation	Adjuvant after surgery	Phase III	OS Disease-free survival	NCT03244384
Atezolizumab 1 yr vs observation	Adjuvant after surgery	Phase III	Disease-free survival	NCT02450331

chemotherapy (20 vs 34% of G3–4 adverse events in the IMVIGOR 211 and 15% vs 49% in the KEYNOTE-045) (Powles et al., 2018a; Bellmunt et al., 2017).

On the contrary, very few data about response to chemotherapy after a treatment with CPIs are available so far. In Cisplatin-ineligible patients who are fit enough to receive CarboGem is it worth to start with CPI monotherapy? At progression after first-line treatment with CPI those patients will probably be in worse conditions and less likely to be fit enough to receive a chemotherapy regimen. With the data available up to now it is not possible to answer this question definitively. Very recently, the results of a retrospective study of 146 Cisplatin-unfit patients treated with chemotherapy followed by immunotherapy or the reverse sequence was presented at 2019 ASCO Conference. No significant difference in OS was detected at the multivariate analysis (HR = 1.05; p = 0.85), and a relevant 44.2% response rate to second line Carboplatin-based chemotherapy was registered, as demonstration that chemotherapy may retain its activity after first line with CPIs (Wei et al., 2019). Although the results presented are surely interesting, there is no information about the number of patients who were treated only with BSC after first-line, and if this number was significantly different between the two groups. For this reason, prospective trials comparing the two different sequences are strongly warranted.

The lack of a direct comparison hampers the use of CPIs in the first line setting also from an economic point of view, because the use of increased resources for these innovative therapies should be justified by robust pharmacoeconomic evaluations of increased efficacy and reduced toxicity (Dranitsaris et al., 2018). In this sense, the recent FDA and EMA warnings have de facto established absence of PD-L1 expression as a key criterion for selection of patients unsuitable to receive first-line Cisplatin, with different tests and cut-offs between different CPIs.

3. Adjuvant setting

Patients not treated with neoadjuvant chemotherapy are potentially eligible for adjuvant treatment after radical cystectomy. Data for adjuvant chemotherapy is not as strong as for the neoadjuvant setting, as the largest randomized phase 3 trial did not show better OS with adjuvant therapy compared with deferred treatment, but only better PFS. After a median follow-up of 7 years, 47% of the patients in the adjuvant group had deceased, compared to 57% of the deferred therapy group (HR = 0.78; 95%CI 0.56–1.08; p = 0.13), while 5-year PFS was significantly improved in the adjuvant group: 47.6% vs 31.8% (HR = 0.54; 95% CI, 0.4 to 0.73; p < 0.0001) (Sternberg et al., 2015). However, the poor accrual limited the power of the study, and it cannot be considered a definitive answer as to whether adjuvant chemotherapy benefits high-risk UC patients (Sonpavde and Pal, 2016).

The largest meta-analysis concerning this issue showed a benefit in OS (HR = 0.77; 95% CI, 0.59 to 0.99; p = 0.049) and disease-free survival (HR = 0.66; 95% CI, 0.45 to 0.91; p = 0.014) for patients treated with adjuvant chemotherapy with a total of 945 patients retrospectively analyzed (Leow et al., 2014a). A similar meta-analysis was also performed for upper tract urothelial carcinoma (UTUC) treated with adjuvant chemotherapy. Although the results showed a benefit in OS for the chemotherapy group (HR = 0.43: 95% CI, 0.21 to 0.89: p = 0.023) it has to be noted that at the time of publication no randomized trial investigating the role of adjuvant chemotherapy for UTUC had been completed (Leow et al., 2014b). Recently, the randomized phase 3 trial POUT, enrolling UTUC patients treated with adjuvant GC vs surveillance after surgery showed a significantly higher disease-free survival in favor of chemotherapy also in this particular setting (2 years DFS 70% vs 51% of the surveillance group; HR = 0.47; 95% CI, 0.3 to 0.59; p = 0.003) (Birtle et al., 2018).

Despite the lack of formally positive randomized trials demonstrating an improvement in OS, adjuvant treatment has become a standard clinical practice in high risk patients not previously treated with neoadjuvant therapy in many countries. Recent data from the adjuvant setting for melanoma showed the possible activity of CPIs even in this context. Ipilimumab in stage III resected melanoma demonstrated in a randomized phase 3 trial a significantly better 5-year recurrence free survival vs placebo (40.8% vs 30.3%; HR = 0.76; 95% CI, 0.64 to 0.89; p < 0.001) and 5-year OS (65.4% vs 54.4%; HR = 0.72; 95% CI, 0.58 to 0.88, p = 0.001) in a randomized phase 3 trial (Eggermont et al., 2016). In the same setting, Pembrolizumab vs placebo demonstrated better 1-year recurrence free survival (75.4% vs 61.0%; HR = 0.57; 98.4% CI, 0.43 to 0.74; p < 0.001) in a randomized phase 3 study (Eggermont et al., 2018). It is possible to hypothesize that CPIs could be active in the adjuvant setting in other immunotherapy-sensitive tumors such as UC, and several trials are ongoing (Table 2), both after surgery and after chemo-radiotherapy (bladder-sparing approaches). To our knowledge, no preliminary results are available so far.

4. Neoadjuvant setting

The exciting results in terms of response and survival of CPIs in the advanced setting increased the interest for the application of these drugs also in the neoadjuvant setting.

The optimal candidate to neoadjuvant chemotherapy is a patient with muscle-invasive (T2-T3) but localized UC, without nodal involvement (cN0) and distant metastases (cM0), and fit to receive a Cisplatin-based regimen (MVAC or CG). Neoadjuvant therapy with three cycles of MVAC demonstrated a clear benefit in median OS (77 vs 46 months) and percentage of patients alive at five years (57 vs 43%; p = 0.006) compared to radical cystectomy alone in a randomized trial with a sample size of 317 patients, while cystectomy alone was associated with an increased risk of death by 33% (HR = 1.33; 95% CI, 1.0–1.76). It was found that survival benefit correlated with the downstaging of the tumor to pT0, a condition occurring in 38% of the patients in the combination therapy group; 85% of whom were alive at 5 years (Grossman et al., 2003). On the basis of the equivalence of efficacy and less toxicity of GC vs MVAC in the advanced setting (Von der Maase et al., 2000) and retrospective neoadjuvant experiences (Dash et al., 2008), GC for three or four cycles has become the most frequently used neoadjuvant regimen even if there are no randomized trial between the two regimens in this setting. If histological complete response is reached, a bladder-sparing therapy with chemo-radiotherapy can be considered in patients who are ineligible for surgery or in those who strongly desire a conservative approach (Meeks et al., 2012).

As neoadjuvant therapy for UC seems to have more solid grounds compared to adjuvant treatments, there was a strong rationale for

Table 3
Neoadiuvant studies with CPIs in urothelial carcinoma.

Intervention	Indication	Phase	Primary endpoint	Trial ID
Pembrolizumab q3w for 3 cycles	Neoadjuvant	Phase II	Pathological complete response rate	NCT02736266
Neoadjuvant Nivolumab with and without Urelumab q2w for 2 cycles	Neoadjuvant	Phase II	Tumor infiltrating CD8 + T cell density at cystectomy	NCT02845323
Ipilimumab w1-4 + Nivolumab w 4 -7	Neoadjuvant	Phase I	Surgical resection < 12 weeks	NCT03387761
Nivolumab d1 + Cisplatin d1 + Gemcitabina d1-8 q3w for 4 cycles	Neoadjuvat	Phase II	Pathological response rate	NCT03294304
Durvalumab + Tremelimuab q4w for 2 cycles	Neoadjuvant	Phase I	Safety	NCT02812420
Pembrolizumab d1 + Cisplatin d1 + Gemcitabine d1-8 q3w for 4 cycles	Neoadjuvat	Phase II	Pathological downstagig (< pT2) rate	NCT02690558
Pembrolizumab q3w in Cisplatin-inelegibile patients	Neoadjuvant	Phase II	Pathological complete response rate	NCT03212651
Cisplatin + Gemcitabine vs Cisplatin + Gemcitabine + Nivolumab + placebo vs Cisplatin + Gemcitabine + Nivolumab + BMS986205	Neoadjuvant	Pahse III	Pathological complete response rate	NCT03661320
Atezolizumab q3w for 2 cycles	Neoadjuvant	Phase II	Pathological complete response rate	NCT02662309
Durvalumab q2w with and without Oleclumab	Neoadjuvant	Phase I	Safety	NCT03773666
Durvalumab + Tremelimumab q28w for 3 cycles vs standard Cisplatin + Gemcitabine or Cisplatin plus Methothrexate, Doxorubicin and Vinblastine	Neoadjuvant	Phase II	Antitumor activity (evidence of pathological residual disease)	NCT03472274
Dose dense Cisplatin plus Methothrexate, Doxorubicin and Vinblastine + Avelumab vs CG + Avelumab vs Paclitaxel + Gemcitabine + Avelumab vs Avelumab	Neoadjuvant	Phase II	Pathologic complete response rate	NCT03674424
Nivolumab q4w for 2 cycles vs Nivolumab + Lirilumab q4w for 2 cycles	Neoadjuvant	Phase I	Safety	NCT03532451

designing neoadjuvant trials with CPIs with the hope of reducing relapses and improving OS at the price of lower toxicity and no increment in surgical complications.

Several clinical studies are ongoing (Table 3), and two ones have already been reported. ABACUS is a single arm, phase 2 neoadjuvant trial with Atezolizumab, administered for 2 cycles before surgery. The main endpoint was a pathologic complete response ratio equal or greater than 20%. Sixty-nine patients were enrolled, and 62 received cystectomy after the neoadjuvant treatment with a promising complete response rate of 29% (18/62 patients). Severe adverse events occurred in 12% of the patients and there was one possible treatment-related death (Powles et al., 2018b).

The second trail named PURE was conducted in Italy. Three cycles of Pembrolizumab were administered after transurethral resection and before radical cystectomy to 50 patients. The most important inclusion criteria were predominantly urothelial histology, clinical stage cT3bN0 or lesser (assessed with CT, MRI or PET/CT), residual disease after TURBT and good general conditions (ECOG PS 0–1). Primary objective was pathologic complete response (pT0) at the time of surgery. All patients underwent radical cystectomy, with 42% of them being pT0. Three patients experienced a grade 3-related adverse event and, of these, only one had to interrupt Pembrolizumab (Necchi et al., 2018).

Many of the actively recruiting neoadjuvant trials explore the combination of CPIs with standard chemotherapy. Few data about combinations are available so far. However, the preliminary results of a combination trial with Pembrolizumab plus CG were presented at ESMO 2018. The main endpoints were safety and pathological non muscle-invasive rate (PAIR). PAIR was promisingly described in 60% of patients, and treatment toxicities were manageable (Hoimes et al., 2018).

The use of CPIs in the neoadjuvant setting appears very interesting, but due to the few data available so far and the lack of comparison with standard chemotherapy, no specific recommendation can be done. Future trials will have to define which is the optimal drug and duration of treatment, as well as to assess potential synergy with chemotherapy and the role of continuing immunotherapy even after surgery.

5. Future prospectives: combination trials and novel targets for immunotherapy

Several ongoing studies are exploring other possible uses of CPIs, the majority of which can be divided into two groups: combination with chemotherapy and combination with another class of CPI.

Despite the common knowledge that chemotherapy has general immunosuppressive effects, the reality is far more complex. Chemotherapy alters the composition and activity of tumor infiltrating lymphoid and myeloid cells in the tumor microenvironment, increasing CD8 T-cells while decreasing regulatory T cells and myeloid-derived suppressive cells. Chemotherapy also augments tumor antigen presentation through MHC-I (Hato et al., 2014). Chemotherapy may therefore enhance the effects of the immune system within the tumor, so many trials have been designed to explore the efficacy of combination of CPIs with cytotoxic drugs in the clinical setting.

In NSCLC patients, the combination of Pembrolizumab and Platinum plus Pemetrexed demonstrated a significantly increased 1-year OS (69.2% vs 49.4%; HR = 0.49; 95% CI, 0.38 to 0.64; $P < 0.001$) and median PFS (median 8.8 months vs 4.9 months; HR = 0.52; 95% CI, 0.43 to 0.64; $P < 0.001$) with no striking differences in severe toxicities (grade 3–4 AES 67.2% vs 65.8%) when compared to chemotherapy plus placebo, respectively, in a pivotal randomized, phase 3 trial, respectively (Gandhi et al., 2018).

The results of a phase 2, single arm trial with a combination of CG plus Ipilimumab (2 cycles of chemotherapy and 4 combination cycles) in UC have already been published, but the trial did not achieve its primary end-point of a 1-year OS > 60% (lower bound of the 90% CI). Yet, the combined regimen showed a remarkable ORR of 69% and a 1-

year OS of 61% (95% CI, 51% - not reached) and a median OS of 13.9 months (95% CI, 10.5–23.4) (Galsky et al., 2018). Other combination studies with Atezolizumab and Pembrolizumab are ongoing. IMVIGOR-130 is a phase 3, multicenter, three-arm, double blind trial of Atezolizumab as monotherapy or in combination with platinum-based chemotherapy compared against chemotherapy plus placebo in patients with locally advanced or metastatic UC previously untreated. KEYNOTE-36 is a phase 3, multicenter, three-arm clinical trial with Pembrolizumab in combination with Platinum-based chemotherapy or in monotherapy, vs standard chemotherapy plus placebo in the first-line setting. The two trials are similar in the design, and at the moment there are not preliminary data.

The combination between two immunotherapeutic agents has also a strong biologic rationale: CTLA-4 and PD1 belong to the same family of co-inhibitory molecules, but they use distinct and non-redundant mechanisms. Both pathways lead to the inhibition of Akt, a key regulator mediator for the production of IL-2, which in turn regulates metabolism and survival of lymphocytes. However, while CTLA-4 inhibits Akt via the protein phosphatase PP2A, preserving the activation of the Phospoinositide 3- kinase (PI3K) pathway. On the contrary, PD-1 inhibits Akt mainly via the PI3K pathway itself. PI3K activates other genes involved in lymphocytes survival and functioning such as Bcl-xL (Parry et al., 2005). Furthermore, inhibition of CTLA-4 increases the activation and proliferation of T-cells, regardless of TCR specificity, and reduces the suppression mediated by regulator T-cells (T-reg), while the inhibition of PD1/PD-L1 interaction restores the activity of peripheral T-cells which have been inactivated by extended antigen exposure (a common event in patient with cancer) (Buchbinder and Desai, 2016). To sum up, CTLA-4 blockade enhances the priming phase of the immune response, while PD-1 blockade works more during the effector phase. Therefore, applying a double block of CTLA-4 and PD-1 can potentiate the activation of the immune system compared to each single block alone.

Firstly, the combination of anti-PD1 and anti-CTLA-4 showed superior activity compared to monotherapy in melanoma patients (Larkin et al., 2015). This combination was also studied in NSCLC (Antonia et al., 2016), in RCC (Motzer et al., 2018) and other tumors, including UC. The multi-arm Phase 1/2 trial CHECKMATE-032 tested the combination of Ipilimumab plus Nivolumab with different doses and Nivolumab alone in multiple solid malignancies, comprising a cohort of UC patients. The results were published very recently: Nivolumab 1 mg/kg plus Ipilimumab 3 mg/Kg combination achieved the highest response rate of 38% in pretreated UC patients, which rose to 58% when only PD-L1 positive patients were considered. The preliminary median OS of this group was interestingly 15.3 months (95% CI, 10.1–27.6), while it was 9.9 months in the Nivolumab 3 mg/Kg arm (95% CI, 7.3–21.1). As expected, there was a relative increase of toxicity in the combination group when compared with the Nivolumab monotherapy arm (39% of grade 3–4 AEs vs 27%, respectively) (Sharma et al., 2019). The Nivolumab plus Ipilimumab combination is currently being tested in the first line setting and compared against the combination of Nivolumab plus standard chemotherapy or chemotherapy alone in the randomized, four-arm CHECKMATE-901 phase III trial.

Another combination of anti-PD1 and anti-CTLA-4 is represented by the association of Durvalumab plus Tremelimumab, which is being studied in terms of safety and efficacy in multiple solid tumors, including UC. Results of the randomized phase III DANUBE study which compares this combination of immunotherapy agents against standard chemotherapy are not yet available (Table 4).

Other targets for immunotherapy are being explored. Among these, some enzymes which produce immunosuppressive agents gained particular interest for their activity. Indolamine-2,3-dioxygenase (IDO) is one of the best known, and a combination of Pembrolizumab and the IDO-inhibitor Epacadostat has been tested in a phase 3 trial for the treatment of metastatic melanoma and RCC. Unfortunately, the combination failed to meet the primary endpoints of OS and PFS as recently announced by Incyte Corporation and Merck (public press 06 April 2018 (Anon, 2019)) and the trials which had been planned to test this combination in many tumors, including UC cohorts, were prematurely closed.

New immune-modulatory enzyme such as CD73, have been identified as possibly druggable targets (Allard et al., 2018) and there is already a phase 1b clinical trial ongoing testing the combination of Pembrolizumab and anti-CD73 in a variety of malignancies, including UC.

6. Concluding remarks

CPI-based immunotherapy is revolutionizing the treatment of UC, although drugs approved by FDA and EMA are still not available in all countries.

For patients with unresectable locally advanced or upfront metastatic disease the best first line of therapy option is still chemotherapy with CG or MVAC. For Cisplatin-ineligible patients, Pembrolizumab and Atezolizumab will probably replace CarboGem in countries where these CPIs have been licensed for this specific indication, provided that their tumor stains positive for PD-L1. CPIs are active and have a good safety profile, but there are no direct comparisons between first-line anti-PD1 / anti-PD-L1 inhibitors and CarboGem.

For second line therapy the options are now broader: Pembrolizumab, Atezolizumab, Nivolumab, Durvalumab or Avelumab appear to achieve long term responses in UC patients, although more than one third of patients may show early progressive disease. Pembrolizumab has the more solid data in this setting, since it is the only drug showing an increase in OS compared to standard chemotherapy in a phase 3 trial. All the CPIs showed less toxicity compared to chemotherapy, and this aspect is particularly relevant for the elderly, in whom the price of toxicity of chemotherapy may be particularly troublesome while the activity of CPIs does not appear to be reduced (Grossi et al., 2018).

Very few data are available on the outcomes of chemotherapy given after CPIs as third and further lines. Yet, we believe that Vinflunine and Paclitaxel may still be options for patients with a good performance status and who are motivated to receive more therapies, especially those patients not responding to CPIs.

In the meantime, the current ongoing chemotherapy/CPIs combination (ChemoCPI) trials are going to raise many new questions. In the near future the choice could be between a ChemoCPI regimen or the sequence of platinum-based chemotherapy followed by CPI in the second line. Moreover, preliminary positive results of Pembrolizumab given as maintenance therapy after response to first line chemotherapy have been presented at ASCO 2019 (Galsky et al., 2019) and some other studies with CPI maintenance are ongoing. OS data from the ChemoCPI trials are still not mature enough to make comparisons with the outcomes of the standard approach of CG in first line and CPIs in second line. If ChemoCPI regimens will be confirmed to be superior to chemotherapy alone with an acceptable safety profile they could probably become the new standard for fit patients, changing for the second time in a few years the landscape of UC treatment.

Furthermore, the anti-PD1 and anti-CTLA-4 combination showed really impressive results in the CHECKMATE-032 in patients pre-treated with platinum-based regimens (Sharma et al., 2019), and this combination is now being tested in the first line setting (CHECKMATE-901). How will we combine ChemoCPI and anti-PD1 and anti-CTLA-4 combination if they both prove to be superior to traditional CG? New randomized and possibly multi-arm trials exploring ChemoCPI vs CPI combination in different sequences would surely be warranted.

In this scenario, the unreliability of PD-L1 as a predictive biomarker for response to CPIs is a major problem and we have also to consider that in the IMVIGOR-211 trial high levels of PD-L1 (assessed on immune cells with VENTANA assay) appeared to predict better response

Table 4
Combined immunotherapy trials in UC.

Intervention	Indication	Phase	Trial ID
Cisplatin + Gemcitabine + Ipilimumab	Unresectable/metastatic	Phase II	NCT01524991
MEDI4736 (anti PD-1) vs MEDI4736 + Tremelimuab vs standard chemotherapy	First-line metastatic	Phase III	NCT025162241
Nivolumab vs Ipilimumab + Nivolumab	Metastatic (multiple neoplasms)	Phase I/II	NCT01928394
Pembrolizumab + chemotherapy	Metastatic	Phase I	NCT02437370
Atezolizumab vs Atezolizumb/placebo + Cisplatin + Gemcitabine	First-line metastatic	Phase III	NCT02807636
CPI-006 (anti-CD73) vs CPI-006 + CPI-444 vs CPI-006 + Pembrolizumab	Metastatic (multiple neoplasms)	Phase I/Ib	NCT03454451
Nivolumab + Ipilimumab/ standard of care chemotherapy vs standard of care chemotherapy	First-line metastatic	Phase III	NCT03036098

to chemotherapy compared to PD-L1 negative patients (Powles et al., 2018a).

As previously described there are different assays and scoring methods to define "PD-L1 positivity". This fact may be source of confusion and conflicting results from different trials and in the second line setting these drugs have indeed been approved regardless of PD-L1 status. In order not to incur in the risk of disparity between patients and to maximize outcomes, it is of primary importance to find a standardized method to assess PD-L1, and to establish its real value as a predictive biomarker.

In addition, it is worthwhile to investigate additional biomarkers, beyond PD-L1, such as the Tumor Mutational Burden (TMB), the presence of deficiency in the mismatch repair (MMR) mechanism, tumor infiltrating lymphocytes, neoantigen burden or immuno-genes signatures (Rizvi et al., 2015; Le et al., 2017; Havel et al., 2019). Some data is available on TMB, which is defined by the total number of mutations found in cancer cells, and has been shown to be associated to tumor response to CPIs in UC and other cancer types (Rosenberg et al., 2016; Chan et al., 2019) but it still need further validation. In addition, cancers with defects of the MMR have been shown to be responsive to Pembrolizumab regardless of their tissue of origin, and this CPI has been approved by FDA in all tumors with this specific alteration (Le et al., 2017).

The pivotal trials for the stage IV UC have shown us that a minority of the patients experience a very durable response to CPIs, while some of them experience a quick progression, the so called hyperprogression: a paradoxical phenomenon of acceleration of tumor growth caused by the administration of CPIs.

Hyperprogression has first been described in melanoma patients, but also some UC cases have been described in the literature. Its prevalence is about 9% in retrospective studies involving multiple neoplasms treated with immunotherapy (Champiat et al., 2017). The biological bases of this particular progression pattern are still being investigated (Wang et al., 2018), and at the moment there are not extensive data about its prevalence in UC patients treated with CPIs. Unfortunately, we do not have any clinical or biological parameter able to predict which patient is at risk of this detrimental effect of immunotherapy.

Another challenge posed by immunotherapy is the phenomenon known as pseudoprogression. In this case, the tumor initially appears to progress from baseline, but stabilizes or responds in following radiological assessments. The real prevalence of this event in UC is still debated: however, it seems to occur from 1.5% to 17% of cases according to retrospective reviews (Soria et al., 2018). Pseudoprogression is thought be a consequence of the infiltration of immune cells within the neoplastic lesions, thus temporary increasing their volume, but there are not definitive answers, yet. New radiology criteria for response evaluation in patients treated with CPIs have been developed, in particular the immune-RECIST (iRECIST) are of help in categorizing pseudoprogression and other peculiar radiological patterns as atypical responses rather than progression (Seymour et al., 2017). It should be noted that most of the information available about these phenomena are from studies involving melanoma, NSCLC and RCC, and they may not be necessarily valid also for UC, but the initial reports and data from the clinical trials seem to confirm that these patterns are associated with this class of drugs (CPIs) and not with the cancer origin. Preliminary data about immunotherapy in the neoadjuvant setting are promising, and the lower toxicity can be an important factor favoring a more widespread use of neoadjuvant treatments before cystectomy, compared to the Cisplatin-based chemotherapy which is still underutilized.

No data are available for the adjuvant setting, but positive results in melanoma patients raise hopes also for UC ones.

The predictable increased use of the much expensive CPIs will probably bring about the problem of affordability and may cause economic stress on the public healthcare systems (Sarfaty et al., 2018). The evaluation of Incremental Cost effectiveness ratio (ICER) of CPIs has urgently to be addressed in the different setting of CU care in which they will be licensed for.

Also, for responder patients the duration of treatment is an important clinical and economical issue. For how long should CPIs be administered in the case of long disease stability, or even complete response? In the clinical trials reviewed for this article, CPIs were administered until progression or unacceptable toxicity. However, in many new trials (especially for melanoma, NSCLC and RCC) there is usually a time limit of two years on treatment. However, in a preliminary report of the CHECKMATE-132 trial, interruption of Nivolumab after one year appeared to be associated with increased risk of early progression (Spiegel et al., 2017). On the contrary, in the phase 3 KEYNOTE-66 trial comparing Ipilimumab vs Pembrolizumab in stage IV melanoma, Pembrolizumab was to be continued until progression or unacceptable toxicity but no more than two years of therapy. Of the patients who completed the two years of Pembrolizumab, 86% were progression free after 20 months (Long et al., 2018), further supporting the idea that treatment holiday in long term responders should be properly studied also in UC patients, because tumors with different biology could behave differently after stopping CPIs.

In conclusion, immunotherapy with CPIs has surely improved the treatment of UC. However, new challenges for clinicians have emerged, especially with regard of choice among different CPIs, patients' selection, management of adverse events, duration of treatment and evaluation of cost-effectiveness of these agents used wither alone or in combination.

Declaration of Competing Interest

Francesco Pierantoni has no conflicts of interest to declare.
Marco Maruzzo has no conflicts of interest to declare.
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