# ADVANCES IN MEDICAL TREATMENTS FOR GENITOURINARY CANCERS

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## ABSTRACT

*Genitourinary (GU) cancers are amongst the most common cancer types, especially neoplasms of the prostate, bladder and kidney. While cure can often only be achieved surgically at early stages, management of advanced or metastatic disease requires systemic medical treatment. With the exception of testicular cancers, systemic therapy of GU cancers has a palliative character and aims to prolong survival and to increase quality of life. With the emergence of molecular targeted therapies such as receptor tyrosine kinase or checkpoint inhibitors, medical management of GU cancers has seen a dramatic progress within the last decade. Moreover, novel combinatorial and sequential therapies have been established thus providing more options for each individual patient but also rendering medical management of urologic tumors more complex. Finally, much progress has been achieved in deciphering the molecular landscapes of GU cancers by next generation sequencing, and novel biomarkers are under investigation to improve patient selection and to optimize systemic therapy.*

*Key words: Prostate cancer, kidney cancer, bladder cancer, chemotherapy, immunotherapy*

## INTRODUCTION

Medical management of urologic malignancies has dramatically changed over the last decade. The introduction of novel substances has improved therapeutic possibilities but has also made clinical-decision making in uro-oncology more complex. With the emergence of targeted immunotherapy (*checkpoint inhibitors*) which were highlighted as the major advance of the year 2017 by the American Society of Clinical Oncology (ASCO), a new class of drugs entered the field of urology.

The introduction of molecular characterization of tumors in recent years using whole transcriptome gene arrays or next-generation sequencing has generated large datasets leading to a new understanding of the genomic landscape of genitourinary (GU) cancers (1). These advances may lead to the identification of novel biomarkers predicting response to therapy as well as druggable targets, and may finally translate into a more tailored approach to the management of cancer patients in uro-oncology.

In this review we will summarize recent developments and discoveries in medical treatment of urological cancers, with a focus on prostate, bladder and kidney cancer.

## UROTHELIAL CANCER

Radical cystectomy (RC) is the standard of care for muscle invasive urothelial cancer. However, almost 50% of the patients with muscle invasive disease develop metastases within 2 years after surgery (2). The chemotherapeutic agent of choice for first line therapy is cisplatin, usually embedded in a regimen combined with gemcitabine due to lower toxicity compared to a combination with methotrexate, vinblastine and doxorubicin (MVAC) resulting in a median survival of 12-16 months (3). However, 30- 50% of patients are ineligible for cisplatin because of poor performance status, renal impairment or other comorbidities. These patients may receive carboplatin-based chemotherapy exhibiting inferior survival rates of about 9.3 months (4).

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As second-line treatments, mainly vinflunine and paclitaxel are used with marginal benefit over best supportive care (5) highlighting the need for novel therapies.

## MODERN IMMUNOTHERAPY CAN BE A GAME CHANGER IN METASTATIC UROTHELIAL CANCER

Immunotherapy has a long history in the treatment of non-metastatic urothelial cancer of the bladder (UCB). In 1976 Alvaro Morales firstly used attenuated mycobacteria as an intravesical therapy of UCB (6). In the following decades a variety of studies could demonstrate a significant impact of Bacillus Calmette-Guérin (BCG) resulting in a decrease of recurrence and progression of localized UCB. Despite all recent progress, BCG remains an established treatment method for patients with non-invasive high-grade UCB.

With the approval of novel immunotherapeutics, a new class of players has entered the field to battle advanced cancer. So-called immune checkpoint proteins are localized on the membrane of T lymphocytes and regulate both activation and inhibition of the immune response. One of the most important regulatory pathways is the interaction between PD-1 the B7.1 receptors and its ligand PD-L1. Tumor cells have the ability to express checkpoint proteins in order to inhibit T-cell mediated immune response. Immune checkpoint inhibitors target the inhibitory signaling pathways between tumor cell and T-cell. This leads to unmasking of tumor cells and their recognition by the immune system and finally resumption of T-cell activity to induce destruction of tumor cells (7). In principle, two different types of monoclonal antibodies are currently applied or clinically investigated for the treatment of GU cancers: PD-1 targeting antibodies such as pembrolizumab and nivolumab or anti-PD-L1 antibodies, atezolizumab, durvalumab or avelumab.

***Atezolizumab*** is a monoclonal anti-PD-L1 antibody that has been approved as a second line therapy after platin-based chemotherapy and as first-line therapy in patients unfit for cisplatin. In the IMvigor-210 trial, a single-arm, multicenter, phase 2 trial, two patient cohorts were investigated (8,9). Cohort 1 comprised patients ineligible for cisplatin while cohort 2 included patients in a second-line setting after platinum-based chemotherapy. Criteria precluding application of cisplatin were glomerular filtration rate lower than 60ml/min, ECOG performance status ≥2, at least grade 2 hearing loss or neuropathy and heart failure NYHA class III or higher. The overall response rate (ORR) in 119 patients in cohort 1 was 23.5% and the overall survival (OS) was 15.9 months. In cohort 2 (310 patients) the ORR was 15% and the median OS was seven months. In a subgroup with higher PD-L1 expression overall response rate was 26% and median OS was 11 months. Surprisingly, it was announced in a press release that the IMvigor 211 phase 3 study comparing atezolizumab with chemotherapy (vinflunine, paclitaxel or docetaxel) in patients with metastastic UCB as second line therapy did not meet its primary endpoint of improved OS. ORR were 13% in both treatment arms. However, median duration of response (DOR) was longer in the atezolizumab arm with 21.7 months compared to 7.4 months in the chemotherapy arm. Grade 3-4 adverse events occurred about as twice as often in the chemotherapy arm compared to atezolizumab (43% vs. 20%). The most common adverse events were fatigue, asthenia, loss of appetite and diarrhea (10). The full publication data are awaited to draw further conclusions.

***Pembrolizumab*** is a humanized monoclonal PD-1 antibody and was approved for second line therapy after chemotherapy and also as a first line immunotherapy for patients unable to receive cisplatin. The Keynote-052 study was a phase 2 single-arm open label study including 370 cisplatin-ineligible patients. 24% of patients showed a response, and 83% of responses were ongoing after 5 months of follow-up. The most common grade 3 or 4 treatment-related adverse events were fatigue (2%), alkaline phosphatase increase (1%], colitis, and muscle weakness (1%) (11).

The phase 3 study (Keynote-045) compared pembrolizumab against conventional chemotherapy (docetaxel, paclitaxel, vinflunine) in 542 patients after platinum-based chemotherapy (12). Patients treated with pembrolizumab had an ORR of 21.1% and a longer median OS compared to chemotherapy (10.3 months versus 7.4 months). Patients in the pembrolizumab arm had a 27% lower risk of death and there were significantly less grade 3 or higher adverse events compared to chemotherapy (15.0% versus 49.4%).

Other checkpoint inhibitors approved for second-line therapy of metastatic UCB are the anti-PD-1 antibody ***nivolumab*** the anti-PD-L1 antibodies ***avelumab*** and ***durvalumab***.

All substances were approved following single arm phase 2 studies. The CheckMate-275 study included 270 patients with metastatic UCB second-line setting. Patients treated with nivolumab showed an ORR of 19.6% and a median OS of 10.3 months (13). Data for avelumab was recently published in a phase 1b study including 44 patients receiving avelumab as a second-line treatment. After a median follow-up of 16.5 months, the ORR was 18.2% while the median duration of response was not reached. The median OS was 13.7 months