# The Role of Immunotherapy in Urologic Cancers

*by Allison May, MD, Loren Roustio, BS & Zachary A Hamilton MD*

**Future studies regarding immunotherapy for these cancers will focus on treatment in the non-metastatic setting.**

Allison May, MD, Loren Roustio, BS, and Zachary A Hamilton, MD, (above), are in the Division of Urology, Department of Surgery, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: zachary.hamilton@health.slu.edu

## Abstract

**In recent decades, there has been significant growth in the understanding of the immune system and its role in cancer. The recent introduction of checkpoint inhibitors has drastically changed the treatment landscape of cancer as a whole. In this review, we discuss the major clinical developments of immunotherapy in urologic specific cancers, as well as address future directions in this field.**

## Introduction

The immune system plays a vital role in cancer prevention and defense. Over the past several decades, immunotherapy has emerged as a treatment option in various urologic malignancies. Recent advances in immunotherapy promise to change the field of urologic oncology substantially. In this review, we aim to summarize the use of immunotherapies for treatment of urothelial, kidney, and prostate cancer.

The roots of immunotherapy in urologic cancers began with the introduction of Bacillus Calmette-Gueren (BCG) for superficial bladder cancer by Morales and colleagues in 1976.[1] This was followed in the 1990s by the introduction of cytokines, such as interferon and IL-2, for metastatic renal cell carcinoma (RCC). The treatment of prostate cancer joined the field of immunotherapy in 2010 with the approval of the autologous cancer vaccine, sipuleucel-T. In more recent years, checkpoint inhibitors have been introduced with dramatic results for urology specific malignancies.

It is helpful to briefly summarize the relationship between the immune system and cancer cells. The immune system constantly scans the body to detect sites of infection and potential cancer cells. In order to prevent erroneous attack on normal cells, the immune system utilizes a series of cellular interactions. T-cell activation requires the engagement of the T-cell receptor (TCR) with the major histocompatibility complex (MHC) on the antigen presenting cell or tumor cell. Activation also requires co-stimulatory signals, namely binding of CD28 on the T-cell with a B7 protein on the antigen presenting cell. At the same time, there are multiple co-inhibitory signals that may take place. Two of the most studied include the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed death 1 (PD-1) pathways, also known as "checkpoints". CTLA-4 is a protein on T-cells that can take the place of CD28 and bind B7, thus resulting in T-cell inhibition. PD-1 is a protein on the T-cell which can bind with programmed death ligand 1 (PD-L1) on tumor or normal cells, leading to down regulation of the T-cell

**Table 1.** Comparison of results of trials for checkpoint inhibitors in metastatic UCC following platinum based chemotherapy.

| Trial | Immunotherapy | ORR |
|---|---|---|
| NCT01375842 | atezolizumab | 11-43%* |
| IMvigor210 | atezolizumab | 15% |
| IMvigor211 | atezolizumab | 62% |
| JAVELIN | avelumab | 16% |
| NCT01693562 | darvalumab | 17% |
| CheckMate 032 | nivolumab | 24% |
| CheckMate 275 | nivolumab | 16 – 28% * |
| KEYNOTE-012 | pembrolizumab | 26% |
| KEYNOTE-045 | pembrolizumab | 21% |

*range based on range of PD-L1 expression

response. These co-inhibitory signals serve as checkpoints to prevent immune attack on normal cells. Cancers avoid attack by taking advantage of these cellular interactions to essentially mask themselves and remain undetected. Checkpoint inhibitors work by preventing these regulatory cellular interactions, thus unmasking the cancer cells.

## Urothelial Cancer

Of all urologic malignancies, urothelial cell carcinoma (UCC) of the bladder and upper tracts has arguably been the most impacted by immunotherapy. The development of BCG for bladder cancer in the 1970s remains a standard of care for treatment of high risk, non-invasive disease in the modern era.[2] In the past several years, checkpoint inhibitors have found notable success in metastatic UCC. Several checkpoint inhibitors are now approved for two main areas of use: in metastatic UCC following standard platinum based chemotherapy, and in metastatic UCC for those deemed 'unfit' for traditional chemotherapy.

## Checkpoint Inhibitors in Metastatic Urothelial Cancer Following Platinum-Based Chemotherapy

Five drugs are currently FDA approved for use in patients with metastatic UCC and progression following platinum based chemotherapy. These include the PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab as well as PD-1 inhibitors nivolumab, and pembrolizumab (Table 1).

Atezolizumab, a PD-L1 inhibitor, was the first checkpoint inhibitor approved in bladder cancer. A phase I trial of 68 patients with previously treated advanced bladder cancer demonstrated an objective response rate (ORR) for atezolizumab of 11% to 43%.[3] Response was highest in patients with high PD-L1 expression (≥5% PD-L1 expression). These results lead to the phase II IMvigor210 trial in which 316 patients with metastatic UCC who had progressed after chemotherapy were treated with atezolizumab.[4] The ORR was 15% overall, compared to 10% in historical controls of alternative chemotherapy regimens, and better response was noted with increasing PD-L1 expression. This led to FDA approval and was later followed by the IMvigor211 phase III study which looked at a similar population of patients with metastatic UCC, including both bladder and upper tract, that had failed traditional platinum based chemotherapy.[5] Patients were randomized to treatment with atezolizumab versus treatment with physician's choice of alternative chemotherapy (paclitaxel, docetaxel, or vinflunine). Overall survival (OS), ORR, and progression free survival (PFS) were not significantly different between the groups, however atezolizumab had an improved safety profile compared to chemotherapy.

Two other PD-L1 inhibitors, avelumab and darvalumab, are FDA approved. Approval for avelumab was based on the UCC cohort of the single-arm, open-label JAVELIN Solid Tumor trial.[6] ORR was 13.3% among 226 patients that were followed for at least 13 weeks and 16.1% for 161 patients that were followed for at least six months. This included an impressive 5.6% complete response rate in the six-month follow up cohort. Traditionally, the ORR rate was poor for alternative chemotherapy regimens and alternative chemotherapy was given for palliation alone, thus a complete response for this patient population garnered considerable excitement amongst clinicians. Interestingly, there was no association found between PD-L1 expression and response. In a similar fashion, darvalumab was approved based on the single-arm phase I/II study 1108.[7] 182 patients were included with an ORR of 17%. Higher PD-L1 expression was associated with better ORR (27.6% in PD-L1 high patients and 5.1% in PD-L1 low or negative).

**Table 2.** Comparison of results of trials for checkpoint inhibitors in metastatic UCC prior to platinum based chemotherapy.

| Trial | Immunotherapy | ORR |
|---|---|---|
| IMvigor210 | atezolizumab | 23% |
| KEYNOTE-052 | pembrolizumab | 24% |

**Table 3.** Comparison of results of trials for checkpoint inhibitors in advanced or metastatic RCC

| Trial | Immunotherapy | ORR |
|---|---|---|
| CheckMate 025 | nivolumab | 25% |
| CheckMate 214 | nivolumab + ipilimumab | 42% |
| KEYNOTE-426 | Pembrolizumab + axitinib | 55.2% |
| JAVELIN Renal 101 | Avelumab + axitinib | 30 – 68%* |

*range based on range of PD-L1 expression

The PD-1 antibody, nivolumab, was approved following the CheckMate 032 and 275 trials for use as second line therapy in metastatic UCC following progression on platinum based therapy. CheckMate 032 was a phase I/II single-arm study which showed an ORR of 24.4% in this patient population.[8] Response rate was not associated with PD-L1 expression, however median OS was higher in patients with high PD-L1 expression. CheckMate 275 was a phase II single-arm study evaluating nivolumab in a similar population and found an ORR of 19%.[9] Furthermore, when stratified by PD-L1 expression the ORR was 28.4% with PD-L1 expression of ≥5%, 23.8% with expression of ≥1%, and 16.1% when expression was <1%.

Another PD-1 antibody, pembrolizumab, achieved FDA approval following the KEYNOTE-012 and KEYNOTE-045 studies. KEYNOTE-012 was a phase Ib study including only patients with ≥1% PD-L1 expression.[10] ORR was 26% in this study. KEYNOTE-045 was a phase III trial comparing pembrolizumab with physician's choice chemotherapy.[11] Improved OS of 10.3 months was found for pembrolizumab compared to 7.4 months for chemotherapy, and the ORR was 21% for pembrolizumab group compared to 11% for chemotherapy. OS was higher for patients with higher PD-L1 expression.

In summary, the use of checkpoint inhibitors for metastatic UCC that has failed traditional platinum based chemotherapy has shown exciting responses when targeting the PD-L/PD-L1 pathway. Most of the five approved therapies show an ORR of ~20% and correlate response with degree of PD-L1 staining. Historically, there was no standard therapy for patients that failed platinum based chemotherapy; however, checkpoint inhibitors are quickly becoming the standard of care in this setting.

## Checkpoint Inhibitors in Metastatic Urothelial Cancer Prior to Platinum-Based Chemotherapy

Checkpoint inhibitors have also been investigated with metastatic UCC that has not received traditional platinum based treatment (Table 2). Atezolizumab was studied in a cohort of the IMvigor210 trial, including patients with metastatic UCC who were ineligible for platinum therapy, with an ORR was 23%.[12] IMVigor130 is an ongoing phase III trial studying treatment naïve patients, including platinum eligible patients. Initial results revealed worsened OS for patients with low PD-L1 expression (<5%) treated with atezolizumab as compared to platinum based therapy.[13] Thus, the FDA has limited use of checkpoint inhibitors as first line therapy only to patients who are ineligible for cisplatin with PD-L1 expression ≥5% or those who are ineligible for any platinum therapy.

Pembrolizumab was studied in the KEYNOTE-052 trial as first line therapy in platinum ineligible patients.[14] ORR was 24% and was higher in those with increased PD-L1 expression. Additionally, the KEYNOTE-361 trial is evaluating pembrolizumab versus pembrolizumab in combination with platinum based chemotherapy versus chemotherapy alone. Similar to atezolizumab, OS was worse compared to chemotherapy for patients with low PD-L1 expression and thus pembrolizumab is only approved for platinum ineligible patients or cisplatin ineligible with higher PD-L1 staining.

## Future Directions in Urothelial Cancer

While bladder cancer has been one of the most responsive tumors to checkpoint inhibitors, only 20-25% of patients treated respond overall in this advanced stage of disease. Thus, trials are underway to investigate use of multiple immunotherapies in combination or combined with chemotherapy in hopes of increasing response rates. Studies are also underway to investigate checkpoint inhibitor use in the non-metastatic setting after primary surgical treatment. In addition, while higher PD-L1 expression tends to favor a response to therapy, patients with minimal PD-L1 expression may still respond. Further research in this area remains ongoing.

**Table 4.** Comparison of results of trials for checkpoint inhibitors in metastatic prostate cancer.

| Trial | Immunotherapy | OS (months) |
|---|---|---|
| IMPACT | Sipuleucel-T | 4.1 |
| KEYNOTE-028 | pembrolizumab | 8.0 |
| CA184-043 | ipilimumab | 6.5 – 22.7 * |
| CA184-095 | ipilimumab | 28.7 |
| CheckMate 650 | Nivolumab + ipilimumab | *Accumulating* |

*range based on high to low risk factors

## Kidney Cancer

Most kidney tumors are resistant to traditional chemotherapy,[15] thus, investigation into alternate therapies for advanced tumors has been well studied in renal cell carcinoma (RCC). The first drug approved for treatment of metastatic RCC (mRCC) was the cytokine interleukin-2. This immunotherapy achieved complete response in a small number of very well-selected patients with minimal comorbidity and limited metastatic burden,[16] however due to its low overall efficacy and severe side effect profile, it has been mostly abandoned. Anti-angiogenic drugs have been developed and widely used, including tyrosine kinase inhibitors such as sunitinib. These targeted agents improve survival, but they have not achieved the complete responses that were historically seen with cytokines. In the past decade, interest towards immunotherapy has surged for RCC, and several checkpoint inhibitors have been approved for advanced or metastatic disease (Table 3).

## Checkpoint Inhibitors in Renal Cell Carcinoma

Nivolumab was the first checkpoint inhibitor approved in kidney cancer. The CheckMate 025 phase III trial compared nivolumab to everolimus in 821 patients with locally advanced or mRCC who had progressed on other therapy.[17] Median OS for nivolumab was 25 months compared to 19.6 months. Interestingly, the improvement in OS was seen regardless of PD-L1 expression in staining. ORR was also higher for nivolumab at 25% versus 5%. Subsequent quality of life assessments noted a change from baseline improved in the nivolumab group which suggested an improvement in quality of life with treatment. This study led to the FDA approval of nivolumab in November 2015 for use in patients with RCC who had previously progressed on one or two regimens of antiangiogenic therapy.

Combination therapies have also been investigated. The IMmotion 150 trial is a phase II trial of 305 patients with advanced or mRCC, randomized to atezolizumab, atezolizumab with bevacizumab, or sunitinib.[18] Patients treated with the combination had improved PFS of 6.1 months compared to either agent alone. This study highlighted the promise of combination immunotherapy in the mRCC setting.

The CheckMate 214 trial assessed the combination use of two checkpoint inhibitors, nivolumab and ipilimumab, as compared to sunitinib.[19] This phase III trial included 1096 patients with advanced or mRCC. Just under half of these patients had poor or intermediate risk disease and all patients had no prior treatment. OS was not reached in the treatment group compared to 28 months for sunitinib and ORR was 42% versus 27% respectively. Those with >1% PD-L1 expression had improved PFS in the treatment arm of 22.8 months versus 5.9 months, as well as improved ORR of 58% versus 22%. Of note, when analysis was done looking at the favorable risk group alone, outcomes were better in the sunitinib group, suggesting the immunotherapy modulated response for mRCC was most significant with more advanced disease. The FDA has now approved nivolumab with ipilimumab in previously untreated advanced RCC with poor or intermediate risk disease.

Additional combination trials have shown benefit for mRCC. The KEYNOTE-426 trial randomized 861 patients with previously untreated advanced RCC to pembrolizumab with axitinib versus sunitinib alone.[20] OS was improved in the pembrolizumab/axitinib arm with 12 month OS of 90% compared to 78%. Median PFS was also improved at 15.1 months versus 11.1 months. This led to FDA approval of pembrolizumab in combination with axitinib in advanced, previously untreated RCC. Similarly, the JAVELIN Renal 101 trial randomized 886 patients with untreated advanced RCC to avelumab with axitinib or sunitinib alone.[21] Improved PFS was noted in the avelumab group of 13.8 months compared to 8.4 months. This led to FDA approval of avelumab with axitinib in advanced untreated RCC.

## Future Directions in Kidney Cancer

Due to the success of checkpoint inhibition for mRCC, particularly with combination therapy, future developments are focused on neoadjuvant treatment for locally advanced disease. The phase III PROSPER trial is underway in which investigators are looking at the use of nivolumab for patients with localized renal masses, who

will be randomized to standard of care surgical therapy versus nivolumab prior to surgery and then continued adjuvantly. All in all, the use of immunotherapy has led to significant advancements for mRCC with promising use of combination therapy.

## Prostate Cancer

The main area of study for immunotherapy in prostate malignancy is with metastatic castrate resistant prostate cancer (mCRPC). Men who develop metastatic disease will eventually progress to castrate resistant disease and fail traditional therapies. At this stage, their disease often becomes lethal with a median OS of 12 months from the time of castrate resistance.[22] Newer therapies have improved survival to an extent, but immunotherapy offers the potential for novel targets in this patient population (Table 4).

Sipuleucel-T was the first, and still the only, immunotherapy approved for prostate cancer and is marketed as a personalized vaccine against prostate cancer. A patient's blood is collected and transferred to an outside facility where antigen presenting cells are harvested from the sample and incubated with sipuleucel-T. The sipuleucel-T is thought to stimulate a T-cell modulated response against prostatic acid phosphatase. The sample can then be infused back into the patient for treatment response.[23] In men with asymptomatic or minimally symptomatic mCRPC, an improvement in OS of 4.1 months was shown in the IMPACT trial.[24] However, due in part to high costs and logistics of infusions, the use remains limited. Additionally, there was a lack of associated PSA response to treatment, making it difficult to determine patient response to therapy. Ongoing trials are examining the use of sipuleucel-T with other immunomodulating agents in a combination fashion, as well as introducing this immunotherapy to men on active surveillance for low risk non-metastatic disease.[25, 26]

PD-1 checkpoint inhibitors have been investigated in prostate cancer, however results to date have not been particularly impressive. A multicenter phase I trial looked at safety and efficacy of Nivolumab in multiple cancers, including advanced prostate cancer.[27] Seventeen men with mCRPR were enrolled and no survival benefit was seen. When tumors from these patients were stained for PD-L1, all were negative. In fact, PD-L1 staining in prostate tumors in general has been shown to be low.[27, 28] The phase Ib KEYNOTE-028 trial evaluated 245 men with mCRPC and included only the 35 who had positive PD-L1 staining ($\geq$ 1%).[29] Twenty-three of these men were treated with pembrolizumab. The ORR was 17% (four patients) and there were no complete responses. Stable disease was achieved in 35%. Median OS for the whole group was eight months and for the patients that responded to therapy was 13 months. Due to the low level of PD-L1 staining and minimal objective response, PD-L checkpoint inhibitors have not yet found a role for prostate cancer.

Two phase III studies investigated the treatment of prostate cancer with ipilimumab, a checkpoint inhibitor of the CTLA-4 pathway. The CA184-043 trial randomized 799 men who had progressed after docetaxel therapy and had undergone bone directed radiotherapy to ipilimumab or placebo.[30] There was no difference in OS. Subset analysis demonstrated lower OS in the ipilimumab group for patients with poor prognostic factors including presence of visceral disease, older age, anemia, elevated alkaline phosphatase and elevated LDH. The CA184-095 trial randomized 598 patients with chemotherapy naïve metastatic prostate cancer with low disease burden to ipilimumab or placebo.[31] Ipilimumab demonstrated no survival benefit.

In an effort to amplify the small benefits seen with prostate cancer utilizing the PD-L1 and CTLA-4 pathways, the CheckMate 650 phase II trial was created for men with mCRPC evaluating the use of nivolumab combined with ipilimumab.[32] An ORR of 26% was achieved in the cohort of patients with no prior chemotherapy and 10% in the cohort with prior chemotherapy. PSA response rates were 18% and 10% respectively. An exploratory biomarker analysis showed a correlation of higher ORR in those with higher tumor mutational burden. Final data is still accumulating for this combination therapy.

In summary, checkpoint inhibitors have shown limited benefit in patients with metastatic prostate cancer, and the responses have not yet outperformed other novel therapies directed at androgen deprivation or androgen signaling pathways. More research is needed to develop genetic and biochemical markers that may identify which patients will respond to immunotherapy. Furthermore, the use of immunotherapy for non-metastatic disease remains unknown.

## Conclusions

Historically, immunotherapy has played an important role in the treatment of urologic malignancies, while in the modern era the development of checkpoint inhibitors has been critical to urology. The introduction of checkpoint

inhibitors has changed the paradigm for treatment of urothelial and kidney cancer. Multiple checkpoint inhibitors are now approved for use in metastatic urothelial cancer following treatment with platinum based chemotherapy, or as frontline in patients not eligible for standard chemotherapy. Additionally, several checkpoint inhibitors are approved for treatment of advanced RCC and show impressive response when used in combination. On the contrary, prostate cancer has found some limited success in the immunotherapy realm with sipuleucel-T; yet, checkpoint inhibition has not yet found a defined treatment role. Future studies regarding immunotherapy for these cancers will focus on treatment in the non-metastatic setting.

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## Disclosure

None reported.

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