Immunotherapy in Urology: The Next Frontier

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T-cell APC interaction. Medical illustration © 2016 by Justin Klein, CMI (see page 8)
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**Introduction**

Immunotherapy is a concept familiar to urologists. From renal cancer to bladder cancer, we have been on the forefront of identifying and adapting opportunities that offer our patients novel approaches to battle disease. In this special supplement to *AUA News* we provide insight to the latest developments in immunotherapy for urological oncology.

Manoj Monga, MD, FACS
Editor, *AUA News*

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**Cancer Immunology 101: What You Need to Know**

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**Case Report**

TF, a 57-year-old electrician, presented in May 2014 with dark urine, 20 lb weight loss, a hemoglobin 7.2 gm/dl and chest pain. He was found to have a small right coronary artery myocardial infarct but a chest radiograph showed multiple pulmonary nodules. Followup computerized tomography showed innumerable lung nodules and a right renal mass. Aspiration biopsy revealed clear cell carcinoma.

The patient was treated with transfusions, aspirin and atorvastin. Anesthesiology refused to clear him for cytoreductive nephrectomy. Therefore, pazopanib was begun and 2 months later, after the iron deficiency anemia resolved, he underwent an uncomplicated coronary artery bypass. Four months after diagnosis and due to persistent gross hematuria with clot retention, cytoreductive nephrectomy was performed (11.7 cm mass), which was complicated by bleeding requiring 6 units of red blood cells. Two months later hypercalcemia developed and positron emission tomography showed modest regression of lung nodules but new lesions in the liver, skin and nodes as well as a lytic lesion in the femur.

The patient underwent orthopedic stabilization of the femur, and received denosumab and radiation to the skin lesion and femur followed by everolimus as second line systemic therapy. Disease progressed in 4 months and he was entered in a clinical trial receiving bezacizumab. Disease again progressed in 2 months with increasing liver and lung lesions, and he was given fourth line axitinib. The patient experienced a 2-month response with reduced pain and stable liver lesions but disease soon rapidly progressed, and new brain metastases developed.

While completing whole brain radiotherapy and with increasing liver lesions, in September 2015 he was started on a new agent, cabozantinib, to which was added after 2 months another new agent, the immune checkpoint inhibitor nivolumab intravenously every 2 weeks. Although the cabozantinib was withheld due to osteonecrosis of the jaw after 11 months, nivolumab continues after 27 doses. All liver lesions have regressed and the lung lesions are significantly smaller (fig. 1). At 2½ years after diagnosis the patient completed a motorcycle trip to South Dakota.

While this case is atypical and administration of the 2 new agents, cabozantinib and nivolumab, in combination was done in desperation, the success for the last year is undeniable.

**Discussion**

Renal cancer has long been known to be immunologically “sensitive,” beginning with numerous case reports of spontaneous regression followed by the use of interferon and then interleukin-2,

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Figure 1. CT of chest before start of nivolumab and cabozantinib (A) and after 6 months of therapy (B).
which was approved by the FDA (U.S. Food and Drug Administration) in 1991. In 2011 Brahmer et al reported the dramatic results of the immune checkpoint inhibiting agent nivolumab against lung and other solid tumors. Prior to that, the immune agent ipilimumab (CTLA-4 [cytotoxic T lymphocyte antigen 4]) revolutionized the treatment of metastatic melanoma, inducing cure in 10% to 20% of patients, leading to FDA approval. When nivolumab was added to ipilimumab, the potential cure rate increased to nearly 40%. Nivolumab is now approved for melanoma, lung cancer (second line), kidney cancer (second line and beyond) and Hodgkin lymphoma. Meanwhile the 2 other immune checkpoint inhibitors that have been FDA approved are atezolizumab for refractory bladder cancer and pembrolizumab for nonsmall cell lung cancer, melanoma, and head and neck cancer. Two other immune checkpoint inhibitors, durvalumab and avelumab, are in phase 3 testing as well. Specifically for renal cancer there are 5 phase 3 trials in treatment naïve patients (see Appendix).

How has this explosion of new drugs and treatment options for renal and bladder cancer come about, and why has it bypassed prostate cancer? Let’s begin with a few basic points about immunology. The 2 branches of the immune system are the innate (composed of macrophages, NK cells and dendritic cells) and the adaptive (composed of B and T cells). The innate side is an immediate response, needs no antigens and has no memory, while the adaptive is a delayed response, requires antigens and has memory. The adaptive immune response has 5 phases that begin with 1) recognition followed in turn by 2) activation and amplification, 3) elimination, 4) contraction and 5) memory. The recognition phase is the responsibility of the macrophages and dendritic/APCs (antigen presenting cells) that present the foreign antigens to the T cells. The activation and amplification phase represents T-cell activation and amplification which is carefully regulated to prevent inappropriate activation. Such T cells can be differentiated into fully activated effector cells. Phase 3 is elimination of the target by the T cells that target the antigens on foreign cells via binding to the MHC complex leading to cell mediated cytotoxicity. Phase 4 is contraction during which the activated T cells are eliminated to protect healthy cells. All T cells express PD-1 (programmed death-1 receptor) and other such receptors so they can be induced into cell death by other immune cells such as dendritic cells that carry PDL-1 (programmed death ligand-1 receptor). These receptors and their ligands are called immune checkpoint inhibitors. A few effector cells survive at low levels to provide long-lasting memory.

In the case of cancer this same process, called the cancer immunity cycle, occurs but is dysregulated at numerous points. In its simplest form tumor antigens are released and engulfed/phagocytized by dendritic cells (fig. 2, 1-2). This activates the dendritic cells to become APCs which present the antigens to T cells. The T cells in turn need to enter the tumor via blood and lymphatic vessels, cause inflammation and theoretically lyse the tumor cells.

Within the tumor microenvironment many factors conspire to inactivate the T cells but most notably many tumor cells up-regulate PDL-1 to activate and kill the invading T cells. Some T cells express B7.1 which also binds to PDL-1, and B7.1 may also inactivate the T cell. A third checkpoint inhibitor is PDL-2 found on normal epithelial cells and APCs. In the tumor microenvironment other immune cells such as macrophages and dendritic cells may (mistakenly?) inactivate T cells. Tumor cells also express cytokines which may further up-regulate PDL-1 to protect against T-cell attack. In turn T cells counterattack with gamma interferon which can kill tumor cells.

Thus, antibodies to PD-1 and PDL-1 strip the tumor cells of a major defense
against T-cell attack. The infiltrating T cells are not as readily inactivated and can induce cell mediated cytotoxicity. Numerous other agents are under development to augment immunological attack on the tumor (fig. 2). A reason that the patient described in the case report had such a good response may have been that he was on cabozantinib, an anti-VEGF agent that enhances T-cell infiltration into tumors (fig. 2, 5). The logic behind the trials listed in the Appendix is in part built on enhancing such T-cell attack. Of course tumors can resist. A recent study showed that melanoma cells resistant to checkpoint inhibitors are deficient in interferon receptor signaling pathways, rendering them resistant to gamma interferon produced by T cells. Another study revealed that melanoma cells and tumors resistant to checkpoint inhibitors expressed beta catenin. Prostate cancer frequently overexpresses WNT/ beta catenin, which may account for the low level of activity of checkpoint inhibitors in prostate cancer.

In conclusion, there are a host of new antibodies that promise to revolutionize the care of patients with urological cancers.

Appendix. First line phase 3 trials for patients with clear cell renal cell carcinoma

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<th>Phase 3 Design</th>
<th>Sponsor</th>
<th>Activity</th>
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<tr>
<td>Atezolizumab plus bevacizumab vs sunitinib</td>
<td>Roche/Genentech</td>
<td>Completed 2016</td>
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<tr>
<td>Nivolumab plus ipilimumab vs sunitinib</td>
<td>Bristol-Myers Squibb</td>
<td>Completed 2015</td>
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<tr>
<td>Pembrolizumab plus axitinib vs sunitinib</td>
<td>Merck</td>
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<td>Pembrolizumab plus lenvatinib vs lenvatinib plus everolimus vs sunitinib</td>
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<td>Avelumab plus axitinib vs sunitinib</td>
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cells by the immune system. Thus, the immune mediated destruction of tumor cells involves infiltration of inflammatory cells into the tumor milieu, and so simple measurements of lesions on computerized tomography may not truly reflect the efficacy of an immune treatment, as it is impossible to distinguish tumor from immune cells with our current imaging technology. This is an important concept that urologists and oncologists will need to incorporate into patient care.

Each of the 7 steps in tumor immune surveillance is mediated by a series of immune checkpoints and cytokines, which regulate immune activity to prevent excessive or prolonged activation. Thus, a mechanism is provided through which excessive or prolonged T-cell activation is avoided and normal tissue is preserved, which may result in tissue destruction and/or autoimmunity. T cells are regulated by a variety of co-stimulatory molecules (CD28 that binds to CD80 or CD86) as well as inhibitory molecules (CTLA-4 that binds to CD80 and CD86), PD-1 and PDL-1. However, up-regulation of PD-1/PDL-1 expression by tumor cells is thought to be a mechanism by which solid tumors evade or develop tolerance to immune regulation. A multitude of other stimulatory and inhibitory ligands and receptors have been identified but to date the CTLA-4 and PD-1/PDL-1 pathways have been the most extensively evaluated in genitourinary malignancies. Humanized monoclonal antibodies (mAbs) that block CTLA-4 (ipilimumab, tremelimumab), PD-1 (nivolumab, pembrolizumab) and PDL-1 (atezolizumab, durvalumab, avelumab) have all demonstrated antitumor responses in patients with bladder and kidney cancer. Activity has been demonstrated with PD-1 and PDL-1 antibodies in patient with metastatic urothelial cancer who had previously been treated with cisplatin based therapy. Atezolizumab, pembrolizumab, nivolumab and durvalumab demonstrate response rates of 16.0%, 27.6%, 24.4% and 31%, respectively, in patients with urothelial cancer regardless of expression of PDL-1 on tumor or immune cells.

An update of the IMVigor 210 trial by Dreicer et al indicates caution when terminating treatment with checkpoint inhibitors too soon. In 310 patients with platinum treated metastatic urothelial carcinoma 1,200 mg atezolizumab was administered intravenously every 3 weeks until loss of clinical benefit. The overall objective response rate using RECIST (Response Evaluation Criteria in Solid Tumors) criteria was 16%, with 28% of patients with moderately or strongly positive stains for PDL-1 in the immune cells demonstrating objective response. What was particularly interesting about this update was the fact that in IMVigor 210 patients were permitted to be treated past progression if the investigator determined that they were gaining clinical benefit from treatment. Of 134 patients who met this criterion at least a 30% reduction in the target lesion was seen on the next radiographic evaluation in 28 (19%).

A similar observation has been made in patients treated with checkpoint inhibition therapy for metastatic renal cancer. Motzer et al randomized 821 patients with metastatic clear cell renal cancer previously treated with a tyrosine kinase inhibitor to 3 mg/kg nivolumab intravenously every 2 weeks or 10 mg everolimus orally once a day. The hazard ratio for death from any cause with nivolumab vs everolimus was HR 0.73 (p=0.002) and objective response rates were nearly fivefold higher with nivolumab (25% vs 5%, p <0.0001). The issue of continued treatment past progression was addressed in this study, as well as in report by Escudier et al. In an ad hoc sensitivity analysis among patients who did not experience disease progression or death by 6 months (35% nivolumab and 31% everolimus) by Motzer et al median progression-free survival (PFS) was 15.6 months with nivolumab vs 11.7 months with everolimus (HR 0.64). The observation that the curves diverged after the median was reached suggests a potential delayed treatment effect with immunotherapy. In the study by Escudier et al overall median duration of treatment was 8.8 months in 38% of 406 patients given nivolumab who were treated past progression and 2.3 months for those who were not treated past progression. From randomization to progression, objective response rate was 20% and 14%, median time to response was 1.9 and 3.7 months, and duration of response was 5.6 and 7.0 months for those who were and were not treated past progression, respectively. Of 140 patients treated past progression with tumor measurements before and after progression 14% had ≥30% tumor burden reduction since first progression. The percentage of patients who had tumor burden reduction past progression is similar to that seen with atezolizumab in bladder cancer.

In conclusion, the classic definitions of response and PFS do not fully capture the efficacy of anti-PD-1 or PDL-1 therapy for urothelial and renal malignancies. This is an important concept for the urologist and the oncologist who may be administering checkpoint inhibition therapy. Careful evaluation of tumor related symptoms, radiographic data, and new imaging techniques are necessary to help better define response and distinguish between true disease progression and pseudo-progression.
Intravesical Immunotherapy for Bladder Cancer

Intravesical immunotherapy in the form of bacillus Calmette-Guérin (BCG) has been the standard of care for patients with intermediate and high risk non-muscle invasive bladder cancer (NMIBC) since its introduction by Morales in 1976.1 On the 40th anniversary of this milestone discovery, systemic immunotherapy in the form of immune checkpoint inhibitors has taken the field of bladder cancer by storm. These agents have proven benefit as second line therapy for advanced urothelial carcinoma2 but they are being tested in all disease states, including NMIBC. In parallel to this intravesical immunotherapy continues to evolve also on other fronts.

Enhancing BCG

Several new developments in intravesical immunotherapy build on the success of BCG as an active therapeutic agent. Rentsch et al demonstrated in a prospective randomized trial that the Connaught strain of BCG was superior to the Tice strain in 142 patients with high risk NMIBC with respect to 5-year recurrence-free survival (74% vs 48%, p=0.01).3 Progression-free (94% vs 88%, p=0.34), disease specific and overall survival (OS) did not differ between strains.

Unfortunately for our patients with NMIBC, Sanofi Pasteur announced on November 17, 2016 that they will permanently discontinue production of the Connaught strain of BCG. The question of differences between strains, however, remains important. A clinical trial will be launched before the end of 2016 under the leadership of SWOG (trial S1602) to test the Tokyo strain of BCG against the Tice strain in patients with high risk NMIBC. If the Tokyo strain proves noninferior, it may facilitate entry of this strain into the North American market.

The S1602 trial from SWOG will ask a second critical question. Preliminary evidence from preclinical models and population studies indicates that vaccination with BCG before intravesical BCG therapy may enhance treatment efficacy.6 In animal models the benefit of priming with vaccination is observed for the Tokyo but not the Tice strain. In the 3 study arms of S1602 patients receive Tice BCG, Tokyo BCG or Tokyo BCG after intradermal BCG vaccination (fig. 1). Vaccination could be a remarkably simple method to improve outcomes.

Another approach to improve BCG is through genetic engineering. BCG acts primarily after uptake into the phagosomes of antigen presenting cells such as macrophages and dendritic cells. The BCG is processed and presented in this manner through the MHC II pathway, which activates primarily CD4 T cells. Better immunogenicity would require presentation with MHC I to CD8 T cells. VPM1002BC is a BCG derived from the Prague subtype of the Danish BCG strain that has been engineered to express the listeria toxin listeriolysin. This pore forming toxin enhances antigen presentation by disrupting lysosomal and cell membranes, and inducing apoptosis in infected cells, thereby leading to better stimulation of CD8 T cells.7 This recombinant BCG has been tested intravesically in a dose escalation phase I trial that revealed no dose limiting toxicity.8 A phase II trial

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SUPPLEMENT ON IMMUNOTHERAPY

**Figure 2. HS410/vesigenurtacel-L mechanism of action** (modified from Heat Biologics).

**Supplement on Immunotherapy**

(NCT02371447) is currently under way through the Swiss Group for Clinical Cancer Research.

The development of MCNA (Mycobacterium phlei cell wall-nucleic acid complex) by Bioniche Life Sciences, Endo Pharmaceuticals and Telesta Therapeutics was an attempt to take advantage of the immunomodulatory mechanisms of BCG while reducing the associated toxicity. MCNA is an agent that contains mycobacterial cell wall fragments and nucleic acid derived from the nonpathogenic Mycobacterium phlei. Although clinical trials have demonstrated activity of MCNA they have not been conducted in a manner that has enabled this agent to obtain FDA (U.S. Food and Drug Administration) approval at this time.

Heat Biologics is developing HS410, also known as Vesigenurtacel-L, as an intradermal vaccine to enhance the effects of intravesical BCG, although it is also being tested as a single agent immunotherapy. HS410 consists of a cancer cell line that has been selected for high expression of some bladder cancer antigens. The cells have been engineered to express high levels of the heat shock protein gp96, which after secretion, delivers the tumor antigens to the antigen presenting cells, which in turn activate a specific antitumor cytotoxic T-cell response (fig. 2). Results of a phase II trial (NCT02010203) of this agent with and without BCG in a mixed population of BCG naïve and BCG recurrent, intermediate and high risk NMIBC cases have been encouraging, and further clinical trials are anticipated.

**Novel Intravesical Immunotherapies**

Two intravesical viral therapies have entered clinical trials on NMIBC. The efficacy of each depends, at least in part, on immunomodulation. Dinney et al from MD Anderson Cancer Center in Houston, Texas developed an adenovirus that expresses recombinant interferon-α2b (rAd-IFN). Interferon is a cytokine that is released by host cells in response to exposure to pathogens but it can also induce tumor cell death through multiple mechanisms. rAd-IFN has been coupled with Syn3, a novel excipient that enhances viral uptake in the bladder wall and transfection into target cells. Transfected cells secrete the interferon-α2b protein. After a single intravesical dose of the agent, therapeutic levels of interferon-α2b can be measured in the bladder for 7 days, which far exceeds what can be achieved with bolus intravesical administration of interferon.

A phase I trial of an intravesically delivered single dose rAd-IFN with Syn3 demonstrated an excellent safety profile and showed early signs of drug activity. A subsequent phase II trial in 40 patients with BCG unresponsive high risk NMIBC revealed a complete response (CR) rate of 50% and a durable 21-month CR rate of 30%. rAd-IFN was re-dosed at 3-month intervals up to 9 months in patients with a CR. A single arm registration trial in the same disease state is currently under way through the Society of Urologic Oncology-Clinical Trials Consortium. Preliminary molecular analyses suggest that combination with a checkpoint inhibitor would be worthy of further study.

The other viral therapy that is currently in clinical trials is the CG0070 virus (Cold Genesys). The genes required for replication of this adenovirus are under the control of the human E2F-1 promoter, which is activated only in cells that have defects in the Rb pathway. Loss of Rb signaling is particularly common in high risk bladder cancer. The virus replicates selectively in these tumors and causes cell lysis with release of virus that can further transfect adjacent cells. The virus is able to spread through the tumor but is incapable of replication outside the tumor.

As an oncolytic virus, the immediate effects of this agent are not strictly dependent on the immune system but the release of tumor antigen likely enhances the antitumor immune response. Furthermore, CG0070 also carries the gene for human granulocyte macrophage-colony stimulating factor, which is a cytokine that has been shown to induce long-lasting specific antitumor immunity in animal models. CG0070 has demonstrated compelling efficacy results in phase I and phase II trials, and is currently being evaluated in a registration trial on BCG unre-
sponsive high risk NMIBC (BOND2, NCT02365818). This trial is specifically studying treatment related changes in PD-L1 expression to establish the rationale for possible combination therapy with a checkpoint inhibitor.

Systemic administration of checkpoint blockers is an exciting strategy for immunotherapy of NMIBC. Three agents are being tested in single arm, phase II trials on BCG unresponsive high risk NMIBC, each following a potential path towards FDA registration (NCT02844816, NCT02901548 and NCT02625961). A potential alternative to systemic administration is intratumoral injection of these agents, which would alleviate concerns for systemic toxicity. van Hooren et al have shown in mouse models of bladder cancer that intratumoral injection of a CTLA-4 inhibitor was as effective as systemic administration in reducing tumor burden but induced lower levels of circulating cytokines (fig. 3).13 Local anti-CTLA-4 therapy in combination with systemic anti-PD-1 therapy resulted in some complete responses and was superior to each therapy alone. A trial strategy is being developed to test this approach in patients with bladder cancer.

While checkpoint blockade fills the headlines, many other highly significant advances are being made with respect to intravesical immunotherapy, which promise to advance the field at least incrementally. BCG therapy is likely to continue to play an important role in the treatment of NMIBC for many years to come.


Figure 3. Intratumoral injection of anti-CTLA-4 in mouse model of bladder cancer. A, tumor before injection. B, needle is visualized in tumor. C, fluid bolus is visualized in tumor after injection.
Thucydides, (460-400 BCE), author of The History of the Peloponnesian War, noted that survivors of the Plague of Athens (430 BCE) could care for the sick without fear of experiencing disease recurrence, and in so doing introduced the concept of immunity. Centuries of investigation have produced a refined understanding of this complex aspect of human physiology, including the differences between the innate (ancient, highly conserved and immediate) and adaptive (acquired, slow, specific, T and B cell mediated) immune systems as well as their relevance to the development of cancer.

Dr. William Coley’s observations in the 19th century connected acute infection (and inflammation) with subsequent tumor regression, and Dr. Lloyd Old provided evidence that immune stimulation by bacillus Calmette-Guérin (BCG) could be used to treat patients with melanoma. Morales introduced urologists to BCG for the treatment of carcinoma in situ of the bladder, and Rosenberg et al demonstrated that the systemic administration of a potent immune modulator, cytokine IL-2, could produce disease regression in a small proportion of patients with renal cell carcinoma and melanoma.

Immunotherapy for cancer became familiar to urologists for the treatment of specific patient populations but the broader potential of this approach would await more specific elucidation of the mechanisms whereby tumors interact with and alter a phenomenon currently known as immune surveillance. Although a variety of immunotherapeutic strategies have been pursued to treat cancer (vaccine therapy, chimeric antigen receptor), recent advances in our understanding of T-cell biology related to specific molecules called checkpoints have resulted in the creation of novel agents that have recently made their way into clinical practice.

The modern era of applied immunomechanics was ushered in by investigators who appreciated that specific T-cell populations provide a continuous surveillance system whereby the body is monitored for and protected against antigens that constitute “danger signals” (“nonself” antigens associated with viruses, bacteria or cancer cells). Danger signals are presented to specific T-cell populations by antigen-presenting cells (APCs), which include macrophages and dendritic cells that express MHC I and II proteins. Antigen presentation stimulates CD4+ (T helper cells) and CD8+ (killer T cells) to coordinate the destruction of targets with exquisite specificity. This paradigm gives rise to a conceptual dilemma. If surveillance is efficient and the adaptive immune system is equipped to eliminate cancer cells as they arise throughout the life of the host, how does a malignant tumor develop? The answer appears to involve understanding how the immune system has evolved to strike a balance between its protective and destructive powers.

That balance is now thought to be achieved, at least in part, through multistep T-cell activation or inhibition elucidated by the pioneering work of many. They showed that 1) APC-MHC complexes are responsible for antigen presentation to T cells and since tumor cells lack MHC or co-stimulatory molecules, they do not stimulate a T-cell dependent, antitumor immune response; 2) tumor cell death results in tumor specific antigen release that can subsequently result in APC presentation in the context of MHC, permitting T-cell receptor antigen interaction,

**Figure.** A, T-cell APC interaction. B, T-cell tumor interaction. Reprinted with permission.
which is the first step in T-cell activation (a process referred to as cross-priming); 3) a second, co-stimulatory step is achieved by interaction of the T-cell surface receptor CD28 with B7 ligands on an APC; and 4) T-cell surface proteins such as CTLA-4 can interact with B7 proteins on the surface of APC to inhibit T-cell activation (part A of figure). Another inhibitory checkpoint elaborated by tumor cells known as PD-L1 can interact with PD-1 on the T cell resulting in inhibition of T-cell activation. The recently reported discovery of a new family of checkpoints, and a growing list of stimulatory and inhibitory cell surface molecules underscore the complexity of T-cell regulation and the opportunity presented by these novel targets for therapeutic intervention (part B of figure). 4,5

The immunogenicity of cancers appears to correlate with the intrinsic quantity of somatic mutations in a given cell. 6 Melanoma, nonsmall cell lung cancer and urothelial bladder cancer are characterized by some of the highest levels of mutational burden of all human malignancies. Somatic mutations are associated with cell surface neo-antigen generation by tumor cells. These antigens are recognized as foreign by APC and T cells. The cytolytic function of T cells (particularly CD8+ T cells) is progressively suppressed as tumor cells induce PDL-1 which interacts negatively with the PD-1 receptor on the T-cell surface. Although the scientific foundation for exploiting this relative “antigenicity” coupled with our new understanding of T-cell activation was laid at the end of the 20th century, it was not until 2010 that checkpoint blocking monoclonal antibodies were shown to improve the survival of patients with cancer. Multicenter studies of patients with metastatic melanoma resulted in FDA (U.S. Food and Drug Administration) approval of the CTLA-4 blocking antibody, ipilimumab, in 2011. Approval of PD-1/PDL-1 blocking antibodies was granted in 2014 for patients with melanoma and lung cancer, and in early 2016 for patients with metastatic urothelial cancer after first line systemic therapy fails. Powles et al, 7 Rosenberg et al, 8 and Tsaiatas and Grivas 9 were among the first to report that the systemic administration of PDL-1 blocking antibodies improved survival in patients with metastatic urothelial cancer. In addition, these investigators noted that the response to systemic PDL-1 blocking antibody was greatest in patients with tumors or tumor infiltrating lymphocytes that expressed PDL-1 by immunohistochemistry (IHC). Rosenberg et al reported that tumor mutational burden predicted response to PDL-1 blockade in their cohort. 8 Reports from several phase 2 trials, CheckMate-275 (Bristol-Myers Squibb) and KEYNOTE-052 (Merck), underscore the activity of immunotherapy in advanced urothelial cancer. The KEYNOTE study is noteworthy because it examined the efficacy of checkpoint blockade in cisplatin ineligible patients. Investigators for this trial have reported a 24% response rate overall and a 37% response rate in patients in whom 10% of tumor cells or tumor infiltrating lymphocytes expressed PDL-1.

Predicting which patients with advanced urothelial cancer are most likely to respond to checkpoint blockade is a matter of ongoing investigation and debate. IHC for the presence of checkpoint molecules in tumor specimens is currently used to identify individuals with a greater likelihood of response but clinical trial data suggest that even patients with low levels or absent checkpoint protein in the tumors may benefit from blockade for reasons that remain obscure. It is possible that the transient expression of checkpoint molecules leads to relative underestimation of their expression in individual tumor specimens. Confounding the matter is lack of agreement among investigators about the clinical significance of different degrees of checkpoint IHC staining. Development of companion biomarkers for the various checkpoint inhibitors will be required to optimize application of these powerful new agents.

Manipulation of the immune system by checkpoint blockade has produced remarkable results in patients with several dire forms of malignancy, including advanced urothelial cancer. Tumors evade destruction when checkpoint molecules are used to circumvent the normal homeostatic influences of the adaptive immune system. As clinicians attempt to restore normal surveillance mechanisms through the administration of blocking antibodies, off-target inflammatory effects have emerged as a new type of treatment associated morbidity known as immune related adverse events (IRAEs). The toxicity associated with checkpoint blockade appears to vary depending on which agent is used but these drugs are generally associated with inflammatory changes that can impact multiple organ systems (fig. 2). 10 Most IRAEs can be managed with steroids and most resolve with treatment. Of importance, since the long-term effects of checkpoint blockade are currently unknown, it will be important to monitor patients for late IRAEs, particularly those who require an extended course of treatment.

Although immune checkpoint inhibitors are being rapidly integrated into management schemes for patients with advanced urothelial cancer, attention has also focused on the relevance of these agents to the treatment of localized disease. Treatment of stage T1-T2 disease with checkpoints in the neoadjuvant setting is under way. These agents may also have a role in trimodality (bladder sparing) protocols in combination with transurethral resection and radiation therapy. Finally, checkpoints are currently under investigation as potential therapy for BCG refractory nonmuscle invasive bladder cancer when administered either systemically or intravesically. 11 The results of these trials are eagerly anticipated by urologists seeking more effective tools for treating patients with this potentially life threatening disease.

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Immunotherapy for Renal Cell Carcinoma

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Renal cell carcinoma (RCC) is the eighth most common cause of cancer in the United States with more than 60,000 new cases diagnosed each year. Approximately a third of the patients present with metastatic RCC (mRCC) requiring systemic therapy. Additionally, of the 70% of patients with localized disease that is amenable to surgical resection 20% to 30% will ultimately have advanced disease requiring systemic therapy. Overall, more than half of the patients with RCC will, at some point during the disease course, require systemic therapy.

Despite significant advancements in the last decade in the development of targeted therapies in the form of vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors, median OS remains relatively poor at 22 to 29 months, and newer agents are sorely needed. The emergence of immunotherapy in the form of immune checkpoint inhibitors that target PD-1, PDL-1 and CTLA-4 has revolutionized the treatment of a variety of cancers in the last few years. The expression and interaction between PD-1 on T cells and PDL-1 on tumor and tumor infiltrating cells can induce inhibition of the immune system, resulting in less effective immuno-surveillance and thus tumor progression. Antibodies against checkpoint inhibitors, eg PD-1, PDL-1 and CTLA-4, serve to overturn this inhibition and reestablish a robust antitumor immune response.2, 3

Role of RCC Immunotherapy

Before the early 2000s, the only FDA (U.S. Food and Drug Administration) approved therapy for mRCC was high dose interleukin-2 (HD IL-2), which was also one of the first immunotherapeutics ever used in oncology. The benefits of HD IL-2 are well established and rest in its ability to lead to a durable response in approximately 5% to 10% of patients.4 Unfortunately, the pro-inflammatory cytokine storm induced by HD IL-2 results in significant toxicity that often requires intensive care unit monitoring. Indeed, the rate of death secondary to IL-2 therapy is as high as 4%.4 As such, despite its ability to produce a long-term response in a small subset of patients, given the relatively high morbidity and rare mortality associated with its use, HD IL-2 treatment is limited to highly specialized centers, and reserved for young patients with good performance status and minimal comorbidities, typically with clear cell histology. A number of models incorporating clinical parameters, disease burden, histology and biomarkers have been investigated to select those patients most likely to benefit from HD IL-2 but currently no uniformly accepted predictive model exists.5

In addition to the relatively infrequently used HD IL-2, immunotherapy with the cytokine interferon-alfa (IFNa) has significant historical precedent in mRCC. However, currently there is no role for IFNa as monotherapy based on studies (notably, CALGB 90206 and AVOREN) that demonstrated superior outcomes when IFNa is combined with bevacizumab compared to the use of IFNa alone. Given the plethora of agents currently approved for mRCC, the role of IFNa as monotherapy or even combined with bevacizumab is currently limited.

Current Update on RCC Immunotherapy

Unlike the high toxicities seen with the use of HD IL-2, immunotherapy with checkpoint inhibitors is far better tolerated. Nivolumab is an IgG4 antibody inhibitor of PD-1 and was the first checkpoint inhibitor to receive FDA approval for the treatment of mRCC. CheckMate 025 was a phase III trial that compared nivolumab to the standard of care everolimus in 821 patients with mRCC and disease progression fol-

*Financial and/or other relationship with Roche/Genentech, Bristol-Myers Squibb, Merck, Exelixis, Astra Zeneca, Dendreon and Bayer.
lowing treatment with VEGF-targeted therapy. The patients were randomized in a 1:1 fashion to receive nivolumab or everolimus. The study met its primary outcome demonstrating superior median OS with nivolumab compared to everolimus (25.0 vs 19.6 months, HR 0.73, 95.99% CI 0.57-.93, p=.002). Similarly, the overall response rates were superior in the nivolumab arm (25% vs 5%, OR 5.98, 95% CI 3.68-9.72, p <.001), while toxicity and quality of life also favored nivolumab. Based on these findings, in November 2015 the FDA approved the use of nivolumab in patients with advanced RCC who had been previously treated with an antiangiogenic agent.

A benefit of immunotherapy is the potential for rapid and durable responses. Although only approximately 25% of patients treated with nivolumab achieve some response, a relatively high proportion of patients demonstrate a sustained response. In phase I and phase II trials of nivolumab for mRCC the survival rates were 41% and 34% at 3 and 5 years, respectively, for 34 patients in the phase I trial, and 35% of 167 patients in phase II were alive at 3 years, suggesting that a subset of responders have a durable response.

Currently, nivolumab remains the only approved immune checkpoint inhibitor for mRCC. However, despite a year since its approval, many questions about its use remain unanswered. For instance, a subset of patients who discontinue nivolumab for toxicity maintain response to therapy despite not actively receiving the drug. This begs the question of the necessary duration of therapy to sustain a response and whether patients need to be indefinitely treated with continuous nivolumab or whether they can be given extended breaks or come off therapy at some point altogether. Similarly, “pseudo-progression” (i.e. early radiographic appearance of progression due to tumor infiltration and not actual tumor growth) can potentially result in patients transitioning to a subsequent line of therapy without the opportunity to potentially benefit further from nivolumab. Therefore, further defining the role of nivolumab continuation at the time of radiological progression is critical and involves multifactorial clinical decision making, which applies in general to immunotherapeutic modalities.

Other questions yet to be answered about nivolumab therapy is the detection of a clear biomarker to predict which patients should be offered a different treatment instead. A number of studies are assessing the immuno-modulatory effects of nivolumab to help prospectively identify biomarkers to predict response but nothing of clinical usefulness has been developed. Importantly, however, PDL-1 expression seems to be prognostic of poorer outcome but was not shown to predict response to nivolumab. More studies are needed to discover and validate putative biomarkers.

**Future Directions for RCC Immunotherapy**

In addition to other areas of interest, the future of immunotherapy for RCC can be divided into 1) assessment of novel immune checkpoint inhibitors; 2) use of checkpoint inhibitors for treatment naïve mRCC as well as in neoadjuvant and adjuvant settings; 3) combinations and/or sequences with other therapies (immunotherapies, targeted or other therapies); 4) potential treatment with anti-PDL-1 after progression on nivolumab; and 5) delineation of inherent and acquired resistance mechanisms to inform future clinical trial designs.

Another novel checkpoint inhibitor currently in development for mRCC is ipilimumab, an anti-CTLA-4 monoclonal antibody. Early studies of ipilimumab in combination with nivolumab demonstrated high response rates and PFS, while a phase III trial (CheckMate 214) with ipilimumab/nivolumab combination vs sunitinib completed enrollment and results are pending. Other immune checkpoint inhibitors in ongoing or completed phase II and III trials for mRCC are the PD-L1 inhibitors atezolizumab (NCT02420821), avelumab (NCT02684006) and durvalumab, and the PD-1 inhibitor pembrolizumab, all of which are being tested either alone or combined with other agents. The role of immune checkpoint blockade in the neoadjuvant and/or adjuvant setting is also being investigated in a number of clinical trials that are industry sponsored, investigator initiated or from cooperative groups (NCT02575222 and NCT0221011). The plethora of immunotherapy trials in mRCC suggests that it is foreseeable that immunotherapy could potentially change the treatment landscape of mRCC, while the development of predictive biomarkers and refined clinical assessment tools may further improve patient selection, clinical use and benefit-to-risk ratio of several agents.

In addition to checkpoint inhibitors and HD IL-2, a potential role remains for immunotherapy with vaccines for RCC. Recently, results of the large phase III trial IMPRoVEd Merritt (IMPROVE, NCT01582672) comparing the multi-epitope cancer vaccine IMAg901 in combination with sunitinib for mRCC demonstrated no OS benefit. However, other vaccines continue to show promise in this setting. The autologous dendritic cell vaccine, AGS-003 demonstrated promising PFS and OS outcomes in a phase II trial. The phase III ADAPT trial comparing sunitinib with or without AGS-003 has completed accrual and results are pending (NCT01582672).

**Conclusions**

It’s an exciting time for immunotherapy in oncology in general and for RCC in particular. With HD IL-2 as an option for select patients and nivolumab as an accepted standard of care after anti-angiogenic therapy, many patients with mRCC are benefiting. Although many questions remain about the currently approved therapies, and the development of additional immunotherapeutics and novel combinations/sequences, the future of immunotherapy for RCC remains bright. Further understanding of RCC molecular biology and immunology is essential, and can support the rationale development of breakthrough treatments.
12 SUPPLEMENT ON IMMUNOTHERAPY

Continued from page 11


Immunotherapy for Prostate Cancer

Susan F. Slovin, MD, PhD, Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, New York

Immunotherapy has taken on a new guise. While initially thought of as largely investigational, it relied heavily on the identification of novel tumor antigens around which the therapy was designed. DNA, viral and carbohydrate vaccines with and without carriers, immune adjuvants or unusual administration platforms such as a gene gun have all met with limited success as have many clinical trials. Ironically, these suboptimal approaches have paved the way toward a better understanding of how the immune system can be altered to facilitate antitumor responses.

Enthusiasm for reexploring immune therapy was debuted with FDA (U.S. Food and Drug Administration) approval of sipuleucel-T (APC 8015) as the first immunotherapy to provide a survival benefit for a solid tumor, prostate cancer. It is an autologous cellular product therapy that capitalizes on the expansion and effector function of dendritic cells (CD54+) (fig. 1).

In the pivotal phase III trial of asymptomatic or minimally symptomatic prostate cancer 352 men were randomized 2:1 in favor of the therapy arm. The cells were incubated with a prostatic acid phosphatase fusion protein coupled with granulocyte macrophage-colony stimulating factor (GM-CSF) and then administered as 3 separate infusions each 2 weeks apart. While generally well tolerated, the most common side effects occurred during infusions and included chills, fatigue, fever, back pain, nausea, joint ache and headache with rare cardiovascular events such as stroke, pulmonary embolus and transient ischemic attacks. Despite the median survival

Figure 1. Overview of dendritic cell (DC) function indicating multiplicity of effector DCs that can influence behavior of T cells including immunity, tolerance and immune deviation. CTL, cytotoxic T lymphocyte. TCR, T-cell receptor. Reprinted with permission from Sousa CR: Nature Rev Imm 2006; 6: 476.
benefit of 4.1 months, minimal or no antitumor responses were seen. The original trials did not follow patients beyond 6 months but, while there might have been some immune enhancement, the development of an antitumor response might have taken longer than anticipated with a cytotoxic agent or a checkpoint inhibitor. This extrapolation was based on observations with checkpoint inhibitors for melanoma which first showed a disease flare on imaging followed by delayed disease regression (see Appendix). This has not been the case for prostate cancer.

However, sipuleucel-T appears to have a subtle impact within the immunologic milieu. There is evidence to suggest that antigen specific T and B cell responses can be generated early, ie after the first infusion, which could be re-stimulated subsequently in vitro. Cytokines associated with T-cell activation were detected and could later be detected in the cell culture fluids following the second and third stimulations. The cytokines, interleukins (IL) 2, 4, 5, 6, 10, 13 and 17, and interferon gamma were detected. Tumor necrosis factor-alpha was also induced. T-cell activation markers CD134 and CD136 on CD4+ and CD8+ T cells were increased after culture with the fusion protein. Recall responses suggestive of sensitivity to the treatment were detected.2, 3

An alternate mechanism of action, antigen spreading (fig. 2), was evaluated by analyzing sera from patients in the phase III IMPACT trial.4 Of the evaluable sera the presence of IgG responses against secondary antigens was consistently observed 3 to 4 months after treatment in the sipuleucel-T arm but not in the control arm. IgG responses against an array of secondary antigens, including an oncogene (K-RAS) and a prostate specific antigen (PSA) (KLK2/hK2), were confirmed in sipuleucel-T treated patients, while responses were not observed in control patients.4 Antigen spread was observed after sipuleucel-T treatment in ProACT, an independent study in patients with metastatic castration-resistant prostate cancer (mCRPC). In IMPACT overall survival was longer for patients treated with sipuleucel-T with IgG response greater than or equal to 2 secondary antigens than in those without such response.4

### Sipuleucel-T

Earlier rather than later? Many urologists have considered exploiting the subtle effects of sipuleucel-T in biochemically relapsed prostate cancer as this therapy may change the immune milieu earlier in the disease process making subsequent therapies more effective. To date, there have been no convincing data to support its earlier use. Attempts to enhance this approach have been made by others including combi-
nation of sipuleucel-T with biological agents such as GM-CSF, chemotherapy or radiopharmaceuticals (fig. 3).

**Immune Platforms**

Despite the enthusiasm for using immunotherapy for prostate cancer, the overall response rates using different platforms have been suboptimal. PROSTVAC, a DNA vaccine comprised of a recombinant vaccinia vector as the primary immunotherapy backbone, has a unique design platform that engenders a more diverse immunological costimulation. It is followed by booster immunization using a recombinant fowlpox vector. The vectors contain transgenes for PSA and “TRICOM,” the latter being 3 co-stimulatory molecules intracellular adhesion molecule-1 (CD54), B7.1 (CD80) and leukocyte function-associated antigen-1 (CD58). Unlike sipuleucel-T, this construct was based on the inherent immunogenicity of the pox virus. An anti-PSA directed T-cell response was generated and other antigens were potentially exposed that could activate other T cells. This was in part thought to be how sipuleucel-T works via antigen spreading. Results of phase I and phase II trials have been encouraging with the phase II trial suggesting a survival benefit comparable to that of sipuleucel-T. The results of the completed pivotal phase III trial are eagerly awaited.

**Checkpoint Inhibitors for Prostate Cancer**

Significant and durable responses have been seen with checkpoint inhibitors used for renal and bladder cancers. Unlike prostate cancer, bladder and kidney cancers have always been thought to have an immune basis for their response to therapies, including the observations of sudden regression of metastatic disease when the primary lesion was removed. In superficial bladder cancer the addition of bacillus Calmette-Guérin (BCG), a weakened bacterial pathogen well known as an immunological adjuvant, has served as an immune modulator. Its mechanism of action is predicated on the generation of a local inflammatory response but new data suggest that there may be more defined mechanisms at play. Bladder cancer is one of several solid tumors, including melanoma, renal cell and nonsmall cell lung cancers, that are hypermutated. Huang et al reported that mutations such as a PTEN deficiency could render multiple types of cells hyper-susceptible to infection by Mycoplasma and BCG. This conclusion was based on the observation that the lipid phosphatase activity of PTEN is required for attenuating infection.

Prostate cancer was the first genitourinary malignancy to be treated with the monoclonal antibody ipilimumab directed against the checkpoint molecule CTLA-4. Ipilimumab was approved for melanoma in the setting of improved survival and antitumor effects. CTLA-4 is a protein receptor that resides within the T cells and down-regulates T-cell function and inhibits excessive expansion of activated T cells acting as a brake.

A phase I/II dose-escalating trial of ipilimumab alone or following radiation to bone lesions, the latter done to induce antigen release, in patients with mCRPC demonstrated safety and tolerability in both arms. A small number of anticipated autoimmune events such as colitis and hypophysitis occurred, regardless of dose, and required treat-

**Figure 4.** Identifying appropriate patient who can benefit from immune therapies remains unclear, although tumor mutational load, intensity of infiltration of intratumoral CD8+ T cells, and expression of PD-1 and PDL-1 may be of benefit as biomarkers of response to checkpoint therapies such as pembrolizumab. As seen in diagram, there is significant functional interrelationship among these factors which may be unique to the individual tumor. Reprinted with permission from Topalian SL, Taube JM, Anders RA et al: Nat Rev Cancer 2016; 16: 275.
ment with high doses of steroids. Most of these events resolved with time but some patients had residual autoimmune disease that mandated permanent dependence on steroids. Several patients sustained durable remissions but a phase III trial of ipilimumab with or without prior radiation in patients after docetaxel failed did not confirm an overall survival benefit (fig. 2). There was also the suggestion that patients with visceral metastases had a worse prognosis and poorer survival.

Benefits of combining ipilimumab with vaccines have been suggested. A recent analysis of the CA184-095 final study results indicated that this randomized, double-blind, phase III trial in asymptomatic or minimally symptomatic patients with mCRPC did not meet its primary end point for OS but demonstrated modest improvements in PFS and PSA response after treatment with ipilimumab versus placebo. Two large randomized trials have now conclusively shown that ipilimumab does not extend OS in unselected populations of patients with mCRPC but results in measurable antitumor activity. Given the selectivity of responses, it may be that unique biomarkers may portend benefit to these drugs (fig. 4).

Recent phase I data indicated activity of the PD-1 checkpoint inhibitor pembrolizumab in patients with mCRPC. Pembrolizumab is a human monoclonal antibody against PD-1 CD279, which is a cell surface receptor expressed on T cells and pro-B cells. PD-1 binds to ligands PDL-1 and PDL-2. PDL-1 is highly expressed on cancer cells and may facilitate cancer immune evasions. Patients with disease progression while on enzalutamide were treated with pembrolizumab every 3 weeks for 4 doses. An early unexpected signal of complete responses was seen in a small number of patients with advanced visceral disease. Activity of this drug in prostate cancer awaits confirmation in larger studies.

Another approach is “armored” or chimeric antigen receptor directed T cells, whereby the patient’s own T cells can be redirected to recognize and kill tumor cells that express a particular antigen on its surface. Significant antitumor responses have been seen in hematologic malignancies but are limited in prostate cancer. In conclusion, immunotherapy is a viable avenue of endeavor that merits continued efforts.

**Appendix. What we need from immuno-therapy**

- Product needs to be off-the-shelf
- Minimal and tolerable side effects
- Reasonable costs
- Anticipated time to treatment effect
- Assessment of biological effect either through standard imaging or relevant biomarkers
- Accountability for possible pseudo-progression

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**Indication**

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**Important Safety Information**

**Serious Adverse Reactions**

Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

**Immune-Related Pneumonitis**

- Immune-mediated pneumonitis or interstitial lung disease, including 2 fatal cases, occurred with TECENTRIQ treatment
- Across clinical trials, 2.6% of patients developed pneumonitis
- Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer steroids for ≥ Grade 2 pneumonitis. Withhold TECENTRIQ until resolution of Grade 2 pneumonitis. Permanently discontinue for Grade 3 or 4 pneumonitis

**Immune-Related Hepatitis**

- Immune-mediated hepatitis, including a fatal case, and liver test abnormalities have occurred with TECENTRIQ treatment
- Across clinical trials, Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%). In patients with urothelial carcinoma (UC), immune-mediated hepatitis occurred in 1.3% of patients
- Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment
- Administer corticosteroids for ≥ Grade 2 transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold TECENTRIQ for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis

PD-L1=programmed death-ligand 1.
Durable responses demonstrated across all patients (median follow-up: 14.4 months)

<table>
<thead>
<tr>
<th>ORR</th>
<th>DoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.8% (n=46/310*; 95% CI, 11.1, 19.3)</td>
<td>(14.4-month median follow-up)</td>
</tr>
<tr>
<td>5.5% CR</td>
<td>9.4% PR</td>
</tr>
</tbody>
</table>

• 22% ORR in patients with disease progression following prior neoadjuvant or adjuvant therapy (n=13/59; 95% CI, 12.3, 34.7)

PD-L1 testing is not required to prescribe TECENTRIQ

IMvigor210 was a Phase II, multicenter, open-label, 2-cohort trial that included a cohort of 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing regimen, or within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant regimen. Patients were treated with TECENTRIQ 1200 mg IV q3w. Major efficacy endpoints included ORR as assessed by IRF using RECIST v1.1 and DoR.1,2

IMvigor210 was a Phase II, multicenter, open-label, 2-cohort trial that included a cohort of 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing regimen, or within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant regimen. Patients were treated with TECENTRIQ 1200 mg IV q3w. Major efficacy endpoints included ORR as assessed by IRF using RECIST v1.1 and DoR.1,2

CI = confidence interval; CR = complete response; DoR = duration of response; IRF = independent review facility; IV = intravenous; ORR = objective response rate; PR = partial response; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

• denotes censored value.

*Number of IRF-assessed confirmed responders.

Important Safety Information (cont’d)

**Immune-Related Colitis**

• Immune-mediated colitis or diarrhea, including a fatal case of diarrhea-associated renal failure, have occurred with TECENTRIQ treatment.

• Across clinical trials, colitis or diarrhea occurred in 19.7% of patients. In UC, immune-mediated colitis or diarrhea occurred in 0.8% of patients.

• Monitor patients for signs and symptoms of diarrhea or colitis. Withhold TECENTRIQ for Grade 2 or Grade 3 diarrhea or colitis. Permanently discontinue for Grade 4 diarrhea or colitis.

**Immune-Related Endocrinopathies**

• Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving TECENTRIQ. Monitor patients for clinical signs and symptoms of endocrinopathies.

• Across clinical trials, hypothyroidism and hyperthyroidism occurred in 3.9% and 1.0% of patients, respectively. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate hormone replacement as needed. Manage isolated hyperthyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed.

• Across clinical trials, adrenal insufficiency occurred in 0.4% of patients. For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer corticosteroids.

• Hypophysitis occurred in 0.2% of patients with UC. Administer corticosteroids and hormone replacement as clinically indicated. Withhold for Grade 2 or Grade 3, and permanently discontinue for Grade 4 hypophysitis.

• New onset diabetes with ketoacidosis occurred in patients. Diabetes mellitus without an alternative etiology occurred in 0.2% of patients with urothelial carcinoma. Initiate treatment with insulin for type 1 diabetes mellitus. For Grade 3 hyperglycemia (fasting glucose ≥250-500 mg/dL), withhold TECENTRIQ.

**Other Immune-Related Adverse Reactions**

• Other immune-related adverse reactions, including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤1.0% of patients treated with TECENTRIQ.

• Symptomatic pancreatitis without an alternative etiology occurred in 0.1% of patients across clinical trials.

• Monitor patients for clinical signs and symptoms of meningitis or encephalitis, as well as symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis or any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome.

• Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ for Grade 3 serum amylase or lipase levels (≥2.0 ULN), or Grade 2 or 3 pancreatitis. Permanently discontinue for Grade 4 or any grade of recurrent pancreatitis.
Recommended dosing and administration

- Do not administer as an IV push or bolus
- Do not co-administer other drugs through the same IV line

Most common adverse events

- The most common adverse events (≥20%) included fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%)
  - Incidence of grade 3 to 4 adverse events included fatigue (6%), decreased appetite (1%), nausea (2%), urinary tract infection (9%), pyrexia (1%), and constipation (0.3%)

Important Safety Information (cont'd)

Infection

- Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage occurred in patients receiving TECENTRIQ
  - Across clinical trials, infections occurred in 38.4% of patients
  - In urothelial carcinoma, infection occurred in 37.7% of patients. Grade 3 or 4 infection occurred in 11.5% of patients, while 3 patients died due to infections. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in 7.3% of patients
  - Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for ≥Grade 3 infection

Infusion-related reactions

- Severe infusion reactions have occurred in patients in clinical trials of TECENTRIQ. Infusion-related reactions occurred in 1.7% in UC
  - Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions

Embryo-Fetal Toxicity

- Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women or women planning to become pregnant of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose of TECENTRIQ

Nursing Mothers

- Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Most Common Adverse Reactions

The most common adverse reactions (rate ≥20%) in UC included fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%).

TECENTRIQ™ (atezolizumab)

Initial U.S. Approval: 2016

This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:

• Have disease progression during or following platinum-containing chemotherapy

2 WARNINGS AND PRECAUTIONS

5.1 Immune-Related Pneumonitis

This indication is approved under accelerated approval based on tumor response rate and duration of response.

4 CONTRAINDICATIONS

[see Clinical Studies (14.1)].

5.2 Immune-Related Hepatitis

[see Warnings and Precautions (5.1)].

5.3 Immune-Related Colitis or diarrhea, defined as requiring use of corticosteroids and with no clear alternate etiology, occurred in patients receiving TECENTRIQ. Liver test abnormalities occurred in patients who received TECENTRIQ. Across clinical trials (n=1,978), Grade 3 or 4 elevation occurred in 2.5% (51/1978) of patients developed pneumonitis. Fatal pneumonitis occurred in two patients. In 523 patients with urothelial carcinoma who received TECENTRIQ, pneumonitis occurred in 5 (1.1%) of patients. Of these patients, there was one patient with fatal pneumonitis, one patient with Grade 3, three patients with Grade 2, and one patient with Grade 1 pneumonitis. TECENTRIQ was held in all cases and five patients were treated with corticosteroids. Pneumonitis resolved in three patients. The median time to onset was 2.6 months (range: 15 days to 4.2 months). The median duration was 15 days (range: 6 days to 3.1+ months).

5.4 Immune-Related Endocrinopathies

[see Warnings and Precautions (5.1)].

6.1 Clinical Trials Experience

The data described in Table 1 reflects exposure to TECENTRIQ in Cohort 2 of Study 1. This cohort consisted of patients with metastatic urothelial carcinoma who had disease progression during or following at least one platinum-based chemotherapy regimen and in 1,787 patients with metastatic urothelial carcinoma in the Phase III IMpower133 trial. A total of 1,787 patients received TECENTRIQ following disease progression during or following platinum-based chemotherapy. The table reflects the percentage of patients with Grade 3 or 4 adverse reactions (ARs) and the number of patients with at least one AR.

6.2 Adverse Reactions

Meningitis / Encephalitis

Motor and Sensory Neuropathy

Pancreatitis

Pneumonitis

6.3 Infusion-Related Reactions

6.4 Embryo-Fetal Toxicity

6.5 Other Immune-Related Adverse Reactions

6.6 Immune-Mediated Endocrinopathies

Hyperthyroidism

Hypothyroidism

Motor and Sensory Neuropathy

Nausea

Diabetes Mellitus

6.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway

6.9 Adrenal Insufficiency

6.10 Infusion-Related Reactions

6.11 Adverse Reactions

6.12 Hypothyroidism

6.13 Hypertension

6.14 Hyperglycemia
common Grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematruia, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia. Three patients (0.9%) who were treated with TECENTRIQ experienced either sepsis, pneumonitis, or intestinal obstruction which led to death. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of the 310 patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 27% of patients; the most common (≥ 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (≥ 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients while Table 2 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of Study 1.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3 – 4 (%)</th>
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</thead>
<tbody>
<tr>
<td>All Adverse Reactions</td>
<td>96</td>
<td>50</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Nausea</td>
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<td>Constipation</td>
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<tr>
<td>General Disorders and Administration</td>
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</tr>
<tr>
<td>Fatigue</td>
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<td>Pyrexia</td>
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<tr>
<td>Peripheral edema</td>
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<td>Infections and Infestations</td>
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<tr>
<td>Urinary tract infection</td>
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<td>9</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
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<td>Decreased appetite</td>
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<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td>Arthritis</td>
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<tr>
<td>Renal and urinary disorders</td>
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<tr>
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<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
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<tr>
<td>Cough</td>
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<td>Skin and Subcutaneous Tissue Disorders</td>
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<tr>
<td>Rash</td>
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<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.3</td>
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<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grades 3 – 4 (%)</th>
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<tr>
<td>Lymphopenia</td>
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<tr>
<td>Hypogammaglobulinemia</td>
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<td>Anemia</td>
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<td>Hyperglycemia</td>
<td>5</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>4</td>
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<tr>
<td>Increased creatinine</td>
<td>3</td>
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<tr>
<td>Increased ALI</td>
<td>2</td>
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<tr>
<td>Increased AST</td>
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<tr>
<td>Hypoalbuminemia</td>
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</tbody>
</table>

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 275 patients in Study 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti–therapeutic antibodies (ATA) at one or more post-dose time points. In Study 1, the presence of ATAs did not appear to have a clinically significant impact on pharmacokinetics, safety, or efficacy. Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of ATAs to TECENTRIQ with the incidence of antibodies to other products may be misleading.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There is no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death [see Data]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal Data**

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

#### 8.2 Lactation

**Risk Summary**

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise a lactating woman not to breastfeed during treatment and for at least 5 months after the last dose.

#### 8.3 Females and Males of Reproductive Potential

**Contraception**

**Females**

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

**Infertility**

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment [see Nonclinical Toxicology (13.1)].

#### 8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

#### 8.5 Geriatric Use

Of the 310 patients with urothelial carcinoma treated with TECENTRIQ in Study 1, 59% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

#### 8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)].

#### 8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of TECENTRIQ is recommended for patients with mild hepatic impairment. TECENTRIQ has not been studied in patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3)].

#### 10 OVERDOSAGE

There is no information on overdose with TECENTRIQ.

#### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-related adverse reactions that may require corticosteroid treatment or interruption or discontinuation of TECENTRIQ, including:

- **Pneumonitis**: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
- **Hepatitis**: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.2)].
- **Colitis**: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.3)].
- **Endocrinopathies**: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis [see Warnings and Precautions (5.4)].
- **Meningoencephalitis, myasthenic syndrome/myasthenia gravis, and Guillain-Barré syndrome**: Advise patients to contact their healthcare provider immediately for signs or symptoms of meningitis, myasthenic syndrome/myasthenia gravis, or Guillain-Barré syndrome [see Warnings and Precautions (5.5)].
- **Ocular Inflammatory Toxicity**: Advise patients to contact their healthcare provider immediately for signs or symptoms of ocular inflammatory toxicity [see Warnings and Precautions (5.5)].
- **Pancreatitis**: Advise patients to contact their healthcare provider immediately for signs and symptoms of pancreatitis [see Warnings and Precautions (5.5)].
- **Infusion-Related Reactions**: Advise patients to contact their healthcare provider immediately for signs and symptoms of infusion-related reactions [see Warnings and Precautions (5.7)].
- **Rash**: Advise patients to contact their healthcare provider immediately for signs or symptoms of rash [see Dosage and Administration (2.2)].

#### Embryo-Fetal Toxicity

Advise female patients that TECENTRIQ can cause fetal harm. Instruct females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ [see Use in Specific Populations (8.1, 8.3)].

#### Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose [see Use in Specific Populations (8.2)].