

Immunotherapy in Urothelial Cancer, Part 2: Adjuvant, Neoadjuvant, and Adjunctive Treatment

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Abstract: Urothelial cancer, which is predominantly seen in men, is common throughout the world. Most disease presents as non-muscle invasive bladder cancer (NMIBC), with cancer recurring or progressing to muscle invasive disease in more than 50% of patients after initial therapy. NMIBC is an immune responsive disease, as indicated by the use of intravesical bacillus Calmette-Guérin as treatment for more than 3 decades. The advent of T-cell checkpoint inhibitors, especially those directed at programmed death 1 (PD-1) and its ligand (PD-L1), has had a significant impact on the therapy of advanced urothelial cancer. This had led to a revisitation of immunotherapy in urothelial cancer, as well as the genesis of trials using novel immunotherapeutic agents. This review focuses on immunotherapy in NMIBC, both on its own and as a potential treatment in combination with RT. It also discusses the development of immunotherapies in early bladder cancer disease states, and in neoadjuvant and adjuvant perioperative settings for localized muscle invasive cancers.

Introduction

Bladder cancer is the sixth most common cancer in the United States. It affects men more often than women, and it affects whites more often than people of other races.¹ Approximately 10% to 20% of non-muscle invasive bladder cancer (NMIBC) progresses to muscle invasive bladder cancer, and 10% to 30% of cases recur.² Stage is the most important independent prognostic variable for assessing the probability of progression and survival. The 5-year survival rate is approximately 77% for all stages of bladder cancer, compared with less than 15% for metastatic bladder cancer.^{3,4} Surgery plus chemotherapy is one standard of care, but effective options have been limited for patients who do not have chemosensitive disease or who cannot receive cisplatin-based chemotherapy. Novel therapies are being explored to give additional options to patients who otherwise would have poor outcomes.

Novel immunotherapies have been developed in recent years for use in a variety of cancers, including bladder cancer. Immunotherapy uses the immune system to recognize and destroy cancer cells.

Intravesical bacillus Calmette-Guérin (BCG), a type of attenuated mycobacterium, was the first type of immunotherapy used to help trigger an immune response, activating immune cells in the bladder as therapy for NMIBC. The US Food and Drug Administration (FDA) approved intravesical BCG in 1990. High-dose interleukin 2 (IL-2) therapy was approved for use in metastatic renal cell cancer and melanoma based on durable complete responses (CRs) in 1995. In 2010, the FDA approved the use of sipuleucel-T (Provenge, Dendreon) immunotherapy for the treatment of early castration-resistant prostate cancer.⁵ Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) was the first immune checkpoint receptor to be clinically targeted, resulting in a survival advantage in patients with advanced melanoma and approval for ipilimumab (Yervoy, Bristol-Myers Squibb) in 2011.^{6,7} More recently, an abundance of research has been conducted on programmed death 1 (PD-1) and its ligand PD-L1, which are part of the family of checkpoint receptors. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms.^{8,9}

PD-L1 is expressed on some tumor cells and many immune cells, and binds to PD-1 on immune cells. The binding of these checkpoint proteins suppresses the immune response. By blocking this interaction, checkpoint inhibitor monoclonal antibodies “release the brakes” on the immune system, allowing immune cells to attack tumors. The T-cell receptor/major histocompatibility complex–antigen complex interacts with the first T-cell activation signal. A second, costimulatory signal from antigen-presenting cells (APCs) is necessary for completion of successful T-cell activation (eg, B7 from APC binding CD28 on the T cell). Without a costimulatory signal, T cells become anergic. After T-cell activation, CTLA-4 expression on the T cell is upregulated, placing a damper on T-cell response. On the APC side, B7-1 and B7-2 are upregulated in inflammatory settings. B7 can be either costimulatory or coinhibitory.¹⁰⁻¹² The net effect is to prevent runaway T-cell activation. PD-1 is also expressed on activated T cells, and expression is induced by inflammatory cytokines at the site of inflammation. PD-1 interacts with PD-L1 on APCs, with the net effect of preventing excessive tissue damage and autoimmunity at the site of infection.¹³ By inhibiting PD-L1, the signals that prevent the body’s immune system from attacking the cancer are lifted.

PD-1– and PD-L1–specific monoclonal antibodies induce tumor regression in patients who have advanced melanoma, refractory Hodgkin lymphoma, renal cancer, lung cancer, and head and neck squamous cell cancer, with very low rates of toxicity. Pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb) were the first checkpoint inhibitors in the anti-PD-1

pathway family to be approved by the FDA for the treatment of refractory melanoma, and atezolizumab (Tecentriq, Genentech) was the first anti-PD-L1 antibody approved for the treatment of metastatic bladder cancer after failure of chemotherapy. PD-1 is a receptor normally involved in downregulating immune responses and promoting peripheral self-tolerance. PD-L1 and PD-L2, which are the 2 main ligands of PD-1, are variably expressed. Many tumors have capitalized on the PD-1/PD-L1 pathway as a mechanism to evade immune surveillance and destruction.¹⁴⁻²⁰ In murine models, expression of PD-L1 on the mastocytoma cell line increased apoptosis in active tumor-reactive T cells, suggesting a possible target for cancer immunotherapy.^{10,20,21} The hypothesis was that exploitation of the PD-1 and PD-L1 pathway in various tumors was a mechanism to evade immune surveillance and destruction. Drugs targeting the PD-1/PD-L1 pathway have led to a greater number of durable responses in selected patients compared with other therapies, such as targeted agents and cytotoxic chemotherapy. In part 1 of this review, we discussed the development of novel T-cell checkpoint inhibitors in advanced or metastatic urothelial cancer.²² In this part, we review the background of immunotherapy in bladder cancer and discuss its evolving role in a variety of bladder cancer disease states, extending from non–muscle invasive to muscle invasive cancer.

Immunotherapy in Non-Muscle Invasive Bladder Cancer

Intravesical immunotherapy has been a mainstay of the treatment of NMIBC for more than 40 years.²³ Intravesical instillation of live BCG reduces both the risk of recurrence and progression to muscle invasive cancer and was granted approval by the FDA in 1990. Multiple randomized trials and meta-analyses have demonstrated superiority of BCG over intravesical chemotherapy regimens or observation.²³ BCG with subsequent intravesical maintenance instillations is the only intravesical regimen so far shown to impact tumor progression in patients with high-risk NMIBC.²⁴⁻²⁷ Current guidelines from the European Association of Urology and the American Urological Association recommend initial weekly intravesical BCG for 6 weeks plus maintenance every 3 months for 1 to 3 years using the SWOG (formerly the Southwest Oncology Group) protocol for patients with high-risk disease (high-grade large or multifocal Ta, any T1, or carcinoma in situ). BCG generally is not recommended for patients with the lowest risk of progression, including those with low-grade Ta primary tumors and those who have infrequent recurrences of small low-grade tumors, which can be treated adequately with transurethral resection and surveillance.^{28,29}

Table 1. Ongoing Trials With Immunotherapy in Non–Muscle Invasive Bladder Cancer

Name and/or Group	Disease State, Arms	Line of Therapy	N	Phase	Identifier
S1602, SWOG	NMIBC: intravesical BCG +/- intradermal BCG prime	First-line: previously untreated	969	3	NCT03091660
WO29635	Atezolizumab with BCG	First-line: previously untreated	18+	1b/2	NCT02792192
University of California, San Francisco	Atezolizumab	First-line: previously untreated; includes muscle invasive and non–muscle invasive bladder cancer	18+	1/2	NCT02451423
S1605, SWOG	Atezolizumab	BCG-refractory NMIBC	153	2	NCT02844816
KEYNOTE-057	Pembrolizumab	BCG-refractory NMIBC	260	2	NCT02625961
Southern Illinois University	Intravenous pembrolizumab, intravesical BCG	First-line	15	1	NCT02324582

BCG, bacillus Calmette–Guérin; NMIBC, non–muscle invasive bladder cancer.

There is no broad consensus on the best approach for patients with high-risk NMIBC in whom BCG is contraindicated, such as patients on immunosuppressants, or those who have had unacceptable side effects from the treatments. BCG can cause flu-like symptoms, fatigue, cystitis, and, occasionally, severe bleeding or bladder contracture. Systemic BCG infection is another, more rare, adverse event. In addition, a significant proportion of patients with high-risk NMIBC will have high-risk tumors that are unresponsive to BCG, including patients with persistent disease after 2 courses (known as BCG-refractory) or those whose disease recurs within 1 year of treatment. Additional BCG is not effective in this setting, but the best next step is unclear because comparative studies of different salvage regimens are lacking. The addition of interferon alfa (IFN- α) to BCG in an attempt to produce heightened immune stimulation has produced mixed results.³⁰ A number of intravesical chemotherapy regimens may be used, including mitomycin C, gemcitabine, docetaxel, and various combinations of these, but all have durable response rates of no more than 20% to 40% in BCG-unresponsive disease.³¹ The only FDA-approved agent in this setting is valrubicin (Valstar, Endo Pharmaceuticals), but the durable response rate to valrubicin at 1 year in patients with BCG-refractory carcinoma in situ is only 10%.³² Cystectomy usually is recommended for patients with high-risk NMIBC that is unresponsive to BCG if they are fit for surgery. However, a large number of patients are poor surgical candidates or refuse this surgery.

In recent years, there has been significant interest in other immunotherapy approaches to NMIBC, and a number of clinical trials are underway or planned. These trials have used a variety of approaches to modulate the

immune system. SWOG is revisiting the role of immunization with intradermal BCG prior to intravesical therapy in S1602 (Different Strains of BCG With or Without Vaccine in High Grade Non-Muscle Invasive Bladder Cancer; NCT03091660). In an effort to stimulate the immune system, patients will receive percutaneous vaccination prior to intravesical instillation of BCG. The percentage of patients with a CR at 3 months following therapy with the TICE percutaneous BCG vaccine vs the standard-protocol intravesical induction BCG vaccine will be analyzed³³

Mycobacteria cell wall extract has been investigated as a potential agent for use in retaining the immune response to BCG without the risk of systemic infection associated with the live bacteria.³⁴ ALT-803 is an IL-15 agonist that is being tested in combination with BCG for NMIBC.³⁵ VMPM1002 bC, a vaccine made from genetically modified mycobacteria bovis, also is being tested both alone and in combination with BCG.³⁶ ALT-801 is a T-cell receptor/IL-2 fusion protein evaluated in a phase 1 trial of patients with BCG-refractory disease.³⁷ PANVAC, a poxvirus-based vaccine therapy targeting CEA and MUC1, is being studied in combination with BCG vs BCG alone for patients with recurrence after at least 1 prior cycle of BCG.³⁸ Finally, rAd-IFN/Syn3 is an adenovirus-mediated gene therapy that induces endogenous production of IFN by the bladder urothelium. It is currently in phase 2 trials.³⁹ Studies on the new checkpoint inhibitors and other immune-based approaches are also being applied to patients with high-risk NMIBC (Table 1). To date, however, the effectiveness is unknown. KEYNOTE-057 (Study of Pembrolizumab in Participants With High Risk Non-Muscle Invasive Bladder Cancer) is a phase 2 trial of pembrolizumab for patients with BCG-unresponsive

disease.⁴⁰ Several other trials are in the planning phases, including one using atezolizumab alone or in combination with BCG.⁴¹ In another trial by SWOG, called S1605 (Atezolizumab in Treating Patients With Recurrent BCG-Unresponsive Non-Muscle Invasive Bladder Cancer), the PD-L1 blocker atezolizumab will be given intravenously to patients who are refractory to BCG. The goal is to control tumor growth and induce responses.⁴² If these studies produce initial promising results, one would expect intense interest in this type of therapy. Such treatments are well tolerated by elderly patients, and avoid the morbidity and quality-of-life impact associated with radical cystectomy.

Combination Immunotherapy and Radiation Therapy

Radiation therapy (RT) generally is not used as the sole primary treatment for bladder cancer, but it may be given in combination with chemotherapy. Another option is trimodality therapy with transurethral resection of bladder tumor (TURBT) followed by chemoradiation. Trimodality therapy is a viable alternative to upfront cystectomy for selected patients who are unwilling or unable to undergo surgery, and has produced similar outcomes in overall survival.⁴³ People who cannot receive chemotherapy may receive RT alone, although this is less effective than RT combined with chemotherapy.⁴⁴

Radiation can induce immunologic-mediated cancer cell death. The immune system plays an important role in promoting the therapeutic effects of radiation. RT causes cancer cell death primarily through DNA damage that leads to cell apoptosis/necrosis. Tumor antigens released from apoptotic tumor cells can provide antigen stimulation that induces an immune response both locally and also at distant metastatic sites. Radiation alone may be insufficient to trigger antigenic signals, and may be augmented by a costimulatory signal to elicit a systemic immune response.⁴⁵ Radiation-induced cell death releases tumor antigens that help prime the antitumor cytotoxic T cells, facilitate tumor antigen uptake by dendritic cells, and promote cross-presentation of tumor antigens on major histocompatibility complex (MHC) class I molecules.^{38,46-50} In addition, radiation helps recruit T cells to tumors by releasing cytokines.⁵¹⁻⁵⁴ These observations have led to preclinical studies on the combination of immunotherapy and RT in multiple tumor models, and clinical studies in metastatic solid tumors, particularly breast cancer and non-small cell lung cancer (NSCLC).^{45,51,55} Breast cancer, colorectal cancer, and glioblastoma cell lines and xenografts have shown improved localized tumor control when anti-CTLA-4 is added to RT.⁵⁶⁻⁵⁸ Use of anti-PD-1 and anti-PD-L1 in combination with RT in the setting

of breast and melanoma mouse xenograft models also has led to improved survival.⁵⁹⁻⁶¹

Radiation, through its immune-stimulating properties, may act as an adjunctive systemic treatment as well as a local treatment. The term *abscopal effect* is used to describe the shrinkage of distant tumors outside the radiation field following the use of radiation to treat a tumor.⁴⁰ Recent progress in the development of tolerable immunotherapy with the potential for combination with RT has moved forward the concept of capitalizing upon the abscopal effect. The combination of anti-CTLA-4 antibodies and RT has shown a benefit in distant disease control in syngeneic mouse models.⁵⁶ Similarly, the combination of RT and anti-PD-1 therapy has led to improvements in response in breast cancer, colorectal cancer, renal cell carcinoma, and melanoma cell line models.^{61,62}

Variables that are involved in the combination of RT and immunotherapy in the laboratory that likely determine successes in the clinical arena are dose, fractionation, and sequencing of treatments. Preclinical data suggest that larger dose per fraction, such as 8 Gy in 3 fractions or 6 Gy in 5 fractions, may be superior to standard fractionation or a single dose of 20 Gy when combined with anti-CTLA-4 blockade. The delivery of CTLA-4 blockade after the completion of RT also has been proven to have a diminished effect compared with concurrent administration.⁵⁶ Concurrent administration is optimal because the use of radiotherapy alone may prime the immune system, allowing antigens to present if the checkpoints are still fully engaged.⁶⁰

Based on results of preclinical studies, RT with immunotherapy has progressed to phase 1/2 clinical trials in multiple disease sites. In a study of patients with melanoma who underwent stereotactic radiosurgery (SRS) for brain metastases, patients who received ipilimumab had a longer median survival than those who did not receive ipilimumab. There was no difference based on whether the drug was given before or after SRS.⁶³ In a multivariate analysis, SRS during ipilimumab treatment was associated with prolonged survival compared with sequential SRS and ipilimumab in metastatic melanoma.⁶⁴ Reports of patients treated with ipilimumab and RT not directed at the central nervous system also have shown promising results in small numbers.⁶⁵ Regression of distant sites of extracranial metastatic melanoma after irradiation and ipilimumab treatment has been reported.⁶⁶ Similar results have been reported in lymphomas, renal cell cancers, and NSCLC.⁶⁷⁻⁶⁹ In addition, response to RT and ipilimumab in patients with castration-resistant prostate cancer occurred without significant adverse events.⁷⁰ Most of the reported abscopal effects have been seen in patients who received RT to a visceral metastasis; therefore, the site of RT may prove to be a variable in the success of combination therapy.⁵¹

Table 2. Ongoing Trials With Immunotherapy in Combination With Radiation Therapy in Bladder Cancer

Disease State, Arms	Line of Therapy	N	Phase	Identifier
Pembrolizumab (anti-PD-1) + hypofractionated RT	Metastatic; progressed after ≥1 regimen of systemic therapy	70	1	NCT02303990
Combining L19-IL2 with SABR	Patients with oligometastatic solid tumors	18	1	NCT02086721
Pembrolizumab, gemcitabine, + concurrent hypofractionated RT	Patients with muscle invasive urothelial cancer who are not candidates for or decline radical cystectomy	54	2	NCT02621151
Pembrolizumab + RT	Group A: Pembrolizumab and RT in locally advanced bladder cancer Group B: Pembrolizumab and RT in metastatic bladder cancer	34	1	NCT02560636

PD-1, programmed death 1; RT, radiation therapy; SABR, stereotactic ablative body radiotherapy.

Although many clinical trials are investigating the synergistic relationship between immunotherapy and RT, mature trials in bladder cancer are lacking. In the setting of bladder cancer, as in other disease sites, the combination of RT and immunotherapy is being examined in patients with metastatic disease but may be especially poignant in urothelial carcinoma (Table 2).⁴⁰

Toxicity of Combination Immunotherapy and Radiation Therapy

With limited clinical experience, there is concern for increased immune-related side effects such as pneumonitis, hepatitis, and colitis when the therapies are delivered together. A retrospective analysis of 29 patients who received extracranial RT and ipilimumab showed no increase in toxicity compared with historical data. The highest doses of RT were associated with RT-induced side effects, but levels were acceptable.^{65,70} Still unknown are the later effects of combining immunotherapy and stereotactic ablative body radiotherapy. The tissue-damaging effects of using radiation at a higher dose per fraction can confer not only acute side effects, but also late effects, such as pneumonitis, in the following months after treatment.

Adjuvant and Neoadjuvant Therapy in Muscle Invasive Bladder Cancer

Muscle invasive bladder cancer has a different and more aggressive biology than NMIBC.⁷¹ Standard treatment in patients with muscle invasive bladder cancer includes cisplatin-based chemotherapy followed by surgical removal of the bladder, or RT and concomitant chemotherapy. Neoadjuvant cisplatin-based chemotherapy prior to cystectomy or RT improves overall survival.^{72,73} Neoadjuvant cisplatin-containing regimens include methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); cisplatin,

methotrexate, and vinblastine (CMV); or gemcitabine and cisplatin (GC). Neoadjuvant studies of MVAC found increased pathological complete response (pCR) rate and improved overall survival at the cost of some short-term toxicity.^{73,74}

Currently, the evidence supporting the use of adjuvant chemotherapy after radical cystectomy is limited. However, in patients with extravesical extension on final pathology after radical cystectomy who are eligible for cisplatin, adjuvant therapy should be considered. The largest phase 3 trial compared immediate vs deferred cisplatin-based combination chemotherapy after radical cystectomy in patients with pT3/pT4 or node-positive urothelial carcinoma of the bladder. In the deferred arm, patients did not receive chemotherapy until relapse. The study resulted in no significant improvement in overall survival with immediate vs deferred chemotherapy after radical cystectomy, although the study may have been underpowered for that primary endpoint.⁷⁵ Several other trials have identified a survival benefit for immediate chemotherapy. This includes the SOGUG (Spanish Oncology Genitourinary Group) 99/01 study using gemcitabine, cisplatin, and paclitaxel, and the ABC (Advanced Bladder Cancer) meta-analysis that suggested a benefit of adjuvant therapy similar to that of neoadjuvant therapy.^{76,77}

In the context of the limited options for patients with renal dysfunction who have poor performance status or whose disease has failed to respond to platinum-based therapy, immunotherapy is being extensively studied in neoadjuvant, adjuvant, recurrent, and advanced bladder cancer. Neoadjuvant chemotherapy is still the preferred method of treatment over adjuvant chemotherapy, and several neoadjuvant immunotherapy trials are underway (Table 3). Two adjuvant trials are in progress: the DN24-02 trial (DN24-02 as Adjuvant Therapy in Subjects With High Risk HER2+ Urothelial Carcinoma), which

Table 3. Neoadjuvant and Adjuvant Immunotherapy Trials in Bladder Cancer

Disease State, Arms	Line of Therapy	N	Phase	Identifier
Neoadjuvant pembrolizumab for muscle invasive bladder cancer (PURE-01)	Neoadjuvant prior to chemoradiation	90	2	NCT02736266
Neoadjuvant pembrolizumab + gemcitabine vs pembrolizumab + gemcitabine/cisplatin	Neoadjuvant	81	Phase 1/2	NCT02365766
Neoadjuvant nivolumab + urelumab vs nivolumab monotherapy	Neoadjuvant	44	2	NCT02845323
Neoadjuvant pembrolizumab + gemcitabine/cisplatin	Neoadjuvant	39	2	NCT02690558
Neoadjuvant atezolizumab (ABACUS)	Neoadjuvant	85	2	NCT02662309
Adjuvant atezolizumab (IMvigor 010/WO29636)	After surgery and/or neoadjuvant chemotherapy	700	3	NCT02450331
Adjuvant nivolumab (CheckMate 274)	After surgery and/or neoadjuvant chemotherapy	640	3	NCT02632409

is examining an autologous cellular immunotherapy product designed to stimulate an immune response in patients with high-risk human epidermal growth factor 2 (HER2)-positive urothelial carcinoma, and the IMvigor 010 trial (A Study of Atezolizumab Versus Observation as Adjuvant Therapy in Participants With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection) of adjuvant atezolizumab, which is designed to clarify the benefits of adjuvant therapy.^{78,79}

As yet, any role for immune checkpoint inhibitor therapy in the neoadjuvant and/or adjuvant setting remains undefined. A randomized phase 3 trial is investigating the addition of adjuvant atezolizumab in patients who had significant residual muscle invasive cancer at cystectomy, and smaller institutional protocols will investigate neoadjuvant use of immune checkpoint inhibitor therapy in patients who are not eligible for cisplatin-based chemotherapy.^{80,81}

For patients with multiple comorbidities or who prefer bladder preservation, a combined-modality approach of TURBT followed by chemoradiotherapy is a valid alternative. Studies investigating the addition of immunotherapy in this patient population are discussed earlier.

Immunotherapy in Rarer Sites and Histological Variants of Urothelial Cancer

Urothelial cancer may occur anywhere in the urinary tract. This includes not only the bladder but also the renal pelvises, ureters, and urethra. These cancers have been included in trials of agents directed at PD-1/PD-L1, so approved agents for urothelial cancers can be used when the primary urothelial cancer site is outside the bladder.

Patients with ureteric carcinoma have an increased chance of harboring genetic microsatellite instability,⁸² which can be detected by immunohistochemistry or next generation genomic profiling of tumor tissue. When microsatellite instability is present, patients have a better response to both chemotherapy and PD-1/PD-L1-directed immunotherapy.

Urothelial cancer may differentiate to variants with phenotypic characteristics that include small cell, squamous cell, adenocarcinoma, sarcomatoid, and trophoblastic appearances. The tumor often consists of a urothelial cancer or in situ carcinoma that differentiates and produces varying amounts of variant cancer. When these variants are in the minority relative to urothelial or transitional cancer, then the tumor generally responds like urothelial cancer. Patients with minority-variant histology have been included in the studies of PD-1/PD-L1-directed immunotherapy, and may respond to it in a similar fashion to cancers that are entirely urothelial. Cases in which the entire tumor has variant differentiation often behave differently than those with pure urothelial cancer, as exemplified by the use of different chemotherapy regimens in them: platin and etoposide in small cell, adding a taxane in squamous cell, and fluoropyrimidine use in adenocarcinomas.⁸³⁻⁸⁵ With regard to immunotherapy directed at T-cell checkpoints in variant histology tumors, there are anecdotal reports of durable response. These agents have activity in small cell, adenocarcinoma, and squamous cell cancers of the lung and head and neck region,⁸⁶⁻⁹⁰ and so may be active in variant urothelial tumors that demonstrate similar histological appearance. To rationalize the use of these expensive drugs, selecting patients for clinical trials

is always appropriate. The use of PD-L1 expression, microsatellite instability, and/or mutational burden may provide justification for selecting these patients for these therapies outside a clinical trial.^{82,91}

Conclusion

The recent advent of PD1/PD-L1–directed immunotherapy has changed urothelial cancer therapy in the advanced setting, particularly for patients whose cancers have progressed on platinum-based therapy or who are not cisplatin-eligible in the first-line metastatic setting. This has the potential to lead to a renaissance of immunotherapy in patients with NMIBC, as well as in the adjuvant, neoadjuvant, and concurrent settings for patients with muscle invasive and locally advanced urothelial cancer. Continued clinical trials are needed to establish the place of these and other immunotherapy agents in the treatment of bladder cancer, and to evaluate their potential to increase CR and cure rates in the non–muscle invasive, localized, and locally advanced settings. Given the therapeutic plateau that existed previously, these new agents are welcome but need to be well-managed for optimal efficacy in early-stage cancer.

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References

1. US Cancer Statistics Working Group. United States Cancer Statistics: 1999–2013 Incidence and Mortality Web-based Report. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2016. <http://www.cdc.gov/uscs>. Accessed November 30, 2016.
2. Youssef RF, Lotan Y. Predictors of outcome of non-muscle-invasive and muscle-invasive bladder cancer. *Scientific World Journal*. 2011;11:369-381.
3. Survival rates for bladder cancer. American Cancer Society. <http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-survival-rates>. Updated May 23, 2016. Accessed January 17, 2017.
4. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol*. 2005;23(21):4602-4608.
5. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.
6. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol*. 2013;13(4):227-242.
7. Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. *Nat Rev Cancer*. 2007;7(2):95-106.
8. Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366(26):2517-2519.
9. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 2005;25(21):9543-9553.
10. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med*. 2002;8(8):793-800.
11. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.
12. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982.
13. Teng MW, Ngiow SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. *Cancer Res*. 2015;75(11):2139-2145.
14. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
15. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28(19):3167-3175.
16. Kozako T, Yoshimitsu M, Fujiwara H, et al. PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients. *Leukemia*. 2009;23(2):375-382.
17. Grzywnowicz M, Zaleska J, Mertens D, et al. Programmed death-1 and its ligand are novel immunotolerant molecules expressed on leukemic B cells in chronic lymphocytic leukemia. *PLoS One*. 2012;7(4):e35178.
18. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MED14736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 2016;34(26):3119-3125.
19. Mok T, Schmid P, Aren O, et al. 192TIP: NEPTUNE: A global, phase 3 study of durvalumab (MED14736) plus tremelimumab combination therapy versus standard of care (SoC) platinum-based chemotherapy in the first-line treatment of patients (pts) with advanced or metastatic NSCLC. *J Thorac Oncol*. 2016;11(4 Suppl):S140-141.
20. Zielinski CC. A phase I study of MEDI4736, NNT-PD-L1 antibody in patients with advanced solid tumors. *Transl Lung Cancer Res*. 2014;3(6):406-407.
21. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. *Semin Oncol*. 2015;42(3):474-483.
22. Yu SS, Dorff TB, Ballas LK, Sadeghi S, Skinner EC, Quinn DI. Immunotherapy in urothelial cancer, part 1: T-cell checkpoint inhibition in advanced or metastatic disease. *Clin Adv Hematol Oncol*. 2017;15(6):466-477.
23. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol*. 1976;116(2):180-183.
24. Kamat AM, Flaig TW, Grossman HB, et al. Expert consensus document: consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer. *Nat Rev Urol*. 2015;12(4):225-235.
25. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol*. 2013;63(3):462-472.
26. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*. 2002;168(5):1964-1970.
27. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*. 2000;163(4):1124-1129.
28. Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71(3):447-461.
29. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol*. 2016;196(4):1021-1029.
30. Rosevear HM, Lightfoot AJ, Birusingh KK, Maymi JL, Nepple KG, O'Donnell MA. Factors affecting response to bacillus Calmette-Guerin plus interferon for urothelial carcinoma in situ. *J Urol*. 2011;186(3):817-823.
31. Ahn JJ, McKiernan JM. New agents for bacillus Calmette-Guerin-refractory bladder cancer. *Urol Clin North Am*. 2013;40(2):219-232.
32. Dinney CP, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients

- with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guerin. *Urol Oncol*. 2013;31(8):1635-1642.
33. ClinicalTrials.gov. PRIME: Pilot Study Evaluating Percutaneous Vaccination of BCG for Bladder Cancer. <https://clinicaltrials.gov/ct2/show/NCT02326168>. Identifier: NCT02326168. Accessed June 9, 2017.
34. Morales A, Phadke K, Steinhoff G. Intravesical mycobacterial cell wall-DNA complex in the treatment of carcinoma in situ of the bladder after standard intravesical therapy has failed. *J Urol*. 2009;181(3):1040-1045.
35. Gomes-Giacoa E, Miyake M, Goodison S, et al. Intravesical ALT-803 and BCG treatment reduces tumor burden in a carcinogen induced bladder cancer rat model; a role for cytokine production and NK cell expansion. *PLoS One*. 2014;9(6):e96705.
36. ClinicalTrials.gov. VPM1002BC in recurrent non-muscle invasive bladder cancer. <https://clinicaltrials.gov/ct2/show/NCT02371447>. Identifier: NCT02371447. Accessed June 9, 2017.
37. Fishman MN, Thompson JA, Pennock GK, et al. Phase I trial of ALT-801, an interleukin-2/T-cell receptor fusion protein targeting p53 (aa264-272)/HLA-A*0201 complex, in patients with advanced malignancies. *Clin Cancer Res*. 2011;17(24):7765-7775.
38. Vasir B, Zarwan C, Ahmad R, et al. Induction of antitumor immunity ex vivo using dendritic cells transduced with fowl pox vector expressing MUC1, CEA, and a triad of costimulatory molecules (rF-PANVAC). *J Immunother*. 2012;35(7):555-569.
39. Navai N, Benedict WF, Zhang G, et al. Phase 1b trial to evaluate tissue response to a second dose of intravesical recombinant adenoviral interferon alpha2b formulated in Syn3 for failures of bacillus Calmette-Guerin (BCG) therapy in nonmuscle invasive bladder cancer. *Ann Surg Oncol*. 2016;23(12):4110-4114.
40. Kamat AM, Bellmunt J, Choueiri TK, et al. KEYNOTE-057: Phase 2 study of pembrolizumab for patients (pts) with bacillus Calmette Guerin (BCG)-unresponsive, high-risk non-muscle-invasive bladder cancer (NMIBC). Poster presented at: 2016 ASCO Annual Meeting; June 3-7, 2016; Chicago, IL. TPS4576.
41. ClinicalTrials.gov. Safety and pharmacology study of atezolizumab alone and in combination with bacille Calmette-Guérin (BCG) in high-risk non-muscle-invasive bladder cancer (NMIBC) participants. <https://clinicaltrials.gov/ct2/show/NCT02792192>. Identifier: NCT02792192. Accessed June 9, 2017.
42. ClinicalTrials.gov. Atezolizumab in treating patients with recurrent BCG-unresponsive non-muscle invasive bladder cancer. <https://clinicaltrials.gov/ct2/show/NCT02844816>. Identifier: NCT02844816. Accessed June 9, 2017.
43. Efsthathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol*. 2012;61(4):705-711.
44. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012;366(16):1477-1488.
45. Tang C, Wang X, Soh H, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? *Cancer Immunol Res*. 2014;2(9):831-838.
46. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol*. 2005;174(12):7516-7523.
47. Neeftjes J, Jongsma ML, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. *Nat Rev Immunol*. 2011;11(12):823-836.
48. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res*. 2015;3(4):345-355.
49. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med*. 2006;203(5):1259-1271.
50. Garnett CT, Palena C, Chakraborty M, Tsang KY, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. *Cancer Res*. 2004;64(21):7985-7994.
51. Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC. Combinations of immunotherapy and radiation in cancer therapy. *Front Oncol*. 2014;4:325.
52. Pilonis KA, Vanpouille-Box C, Demaria S. Combination of radiotherapy and immune checkpoint inhibitors. *Semin Radiat Oncol*. 2015;25(1):28-33.
53. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res*. 2014;74(19):5458-5468.
54. Bernstein MB, Garnett CT, Zhang H, et al. Radiation-induced modulation of costimulatory and coinhibitory T-cell signaling molecules on human prostate carcinoma cells promotes productive antitumor immune interactions. *Cancer Biother Radiopharm*. 2014;29(4):153-161.
55. Gridelli C, Ascierto PA, Barberis MC, et al. Immunotherapy of non-small cell lung cancer: report from an international experts panel meeting of the Italian association of thoracic oncology. *Expert Opin Biol Ther*. 2016;16(12):1479-1489.
56. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res*. 2009;15(17):5379-5388.
57. Demaria S, Pilonis KA, Vanpouille-Box C, Golden EB, Formenti SC. The optimal partnership of radiation and immunotherapy: from preclinical studies to clinical translation. *Radiat Res*. 2014;182(2):170-181.
58. Belcaid Z, Phallen JA, Zeng J, et al. Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model. *PLoS One*. 2014;9(7):e101764.
59. Zeng J, See AP, Phallen J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys*. 2013;86(2):343-349.
60. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16(13):e498-509.
61. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124(2):687-695.
62. Duong CP, Yong CS, Kershaw MH, Slaney CY, Darcy PK. Cancer immunotherapy utilizing gene-modified T cells: from the bench to the clinic. *Mol Immunol*. 2015;67(2 Pt A):46-57.
63. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg*. 2012;117(2):227-233.
64. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys*. 2015;92(2):368-375.
65. Barker CA, Postow MA. Combinations of radiation therapy and immunotherapy for melanoma: a review of clinical outcomes. *Int J Radiat Oncol Biol Phys*. 2014;88(5):986-997.
66. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. *Oncimmunology*. 2014;3:e28780.
67. Wersall PJ, Blomgren H, Pisa P, Lax I, Kalkner KM, Svedman C. Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. *Acta Oncol*. 2006;45(4):493-497.
68. Robin HI, AuBuchon J, Varanasi VR, Weinstein AB. The abscopal effect: demonstration in lymphomatous involvement of kidneys. *Med Pediatr Oncol*. 1981;9(5):473-476.
69. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res*. 2013;1(6):365-372.
70. Slovin SE, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol*. 2013;24(7):1813-1821.
71. Kamat AM, Agarwal P, Bivalacqua T, et al. Collaborating to Move Research Forward: Proceedings of the 10th Annual Bladder Cancer Think Tank. *Bl Cancer*. 2016;2(2):203-213.
72. Porter MP, Kerrigan MC, Donato BM, Ramsey SD. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol*. 2011;29(3):252-258.
73. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol*. 2011;29(16):2171-2177.
74. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer*. 2011;117(2):276-282.
75. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol*. 2015;16(1):76-86.
76. Paz-Ares LG, Solsona E, Esteban E, et al. Randomized phase III trial comparing adjuvant /gemcitabine/cisplatin (PGC) to observation in patients with resected

- invasive bladder cancer: results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study [ASCO abstract LBA4518]. *J Clin Oncol*. 2010;28(18) (suppl).
77. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) meta-analysis collaboration. *Eur Urol*. 2005;48(2):189-199.
78. ClinicalTrials.gov. DN24-02 as Adjuvant Therapy in Subjects With High Risk HER2+ Urothelial Carcinoma. 2015; US National Library of Medicine. Available at: <https://clinicaltrials.gov/ct2/show/NCT01353222>. Identifier: NCT01353222. Accessed June 9, 2017.
79. ClinicalTrials.gov. A phase III study of atezolizumab treatment versus observation as adjuvant therapy in patients with PD-L1 positive, high risk muscle invasive bladder cancer after cystectomy (IMvigor010). <https://clinicaltrials.gov/ct2/show/NCT02450331>. Identifier: NCT02450331. Accessed June 9, 2017.
80. ClinicalTrials.gov. A study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer [IMvigor210]. <https://clinicaltrials.gov/ct2/show/NCT02108652>. Identifier: NCT02450331. Accessed June 9, 2017.
81. ClinicalTrials.gov. Testing the PD-1 inhibitor pembrolizumab as maintenance therapy after initial chemotherapy in metastatic bladder cancer. <https://clinicaltrials.gov/ct2/show/NCT02500121>. Identifier: NCT02500121. Accessed June 9, 2017.
82. Lee V, Murphy A, Le DT, Diaz LA, Jr. Mismatch repair deficiency and response to immune checkpoint blockade. *Oncologist*. 2016;21(10):1200-1211.
83. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. *J Urol*. 2004;172(2):481-484.
84. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol*. 2001;19(9):2527-2533.
85. Siefker-Radtke A. Urachal carcinoma: surgical and chemotherapeutic options. *Expert Rev Anticancer Ther*. 2006;6(12):1715-1721.
86. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.
87. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135.
88. Carbognin L, Pilotto S, Milella M, et al. Differential activity of nivolumab, pembrolizumab and MPDL3280A according to the tumor expression of programmed death-ligand-1 (PD-L1): sensitivity analysis of trials in melanoma, lung and genitourinary cancers. *PLoS One*. 2015;10(6):e0130142.
89. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.
90. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128.
91. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387(10031):1909-1920.

Erratum

An article in the May 2017 issue, “Non–Clear Cell Renal Cell Carcinomas: Biological Insights and Therapeutic Challenges and Opportunities” by Gabriel G. Malouf, MD, Richard W. Joseph, MD, Amishi Y. Shah, MD, and Nizar M. Tannir, MD, listed the final chemotherapy regimen in Table 2 on page 414 as “Pemetrexed plus capecitabine” when it should have read “Pemetrexed plus gemcitabine.” The corrected article has been posted to the online version at www.hematologyandoncology.net.