



Perioperative immunotherapy in muscle-invasive bladder cancer

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Abstract: Muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC) are both major causes of morbidity and mortality. At diagnosis, MIBC is more likely to metastasize, but can often be treated with aggressive care. Standard treatment for MIBC patients is radical cystectomy but a select group of these individuals are not candidates for or will decline this treatment. Thus, bladder preservation therapy followed by combined chemoradiation may be considered. Despite the primary surgical management of MIBC, up to half of patients will obtain tumors at distant sites in the end and perioperative platinum-based chemotherapy comprises the standard of care. However, despite these aggressive treatment options, survival is poor and therefore, it is essential to combine local and systemic therapies. Therapeutic modalities contained cancer vaccines, immune checkpoint inhibitors and immunogenic therapy are emerging as alternatives to immunotherapy, and several drugs have recently been approved by the FDA. Currently, several trials of adjuvant immunotherapy based on checkpoint inhibitors that as monotherapy, inhibit the reaction between programmed death-receptor 1 (PD-1) and programmed death-receptor ligand 1 (PD-L1). Or combined therapies mixed with chemotherapy, radiation, or various immunotherapy are ongoing. This review summarizes the current state of immunotherapies and evolution of the chemotherapy landscape for MIBC perioperative treatment. Widespread research is currently being performed to investigate the role of perioperative immune checkpoint inhibition in both the neoadjuvant and adjuvant setting.

Keywords: Chemotherapy; muscle-invasive bladder cancer (MIBC); immune checkpoint inhibitors (ICPIs); programmed death-receptor 1 (PD-1); programmed death-receptor ligand 1 (PD-L1)

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Introduction

The incidence of bladder cancer, which is more often observed in men, is increasing in the developed countries. The most likely risk factor is smoking (1). Generally, this disease classified as three disease states, namely non-muscle-invasive, muscle-invasive, or metastatic. Non-muscle-invasive bladder cancer (NMIBC) can involve the mucosa (Ta), submucosa, or lamina propria (T1); alternatively, it can comprise flat carcinoma in situ (CIS). Moreover, of all bladder cancer patients, 70% of patients are diagnosed with

NMIBC and the rest are diagnosed with muscle-invasive (MIBC) or metastatic disease (2). Bladder cancer, comprising a heterogeneous epithelial malignancy, most commonly presents as exophytic tumors which are confined to the mucosa or lamina propria. However, at initial diagnosis, 25% of patients have MIBC or metastatic disease, which is associated with worse prognosis. Accordingly, NMIBC and MIBC are both major causes of morbidity and mortality. Whereas radical cystectomy comprises the standard care for MIBC patients, some of these individuals (clinical stage T2 unifocal tumor, status-post-complete transurethral bladder

tumor resection (TURBT), no hydronephrosis, no CIS, and good baseline bladder function) will not be candidates for or might decline this treatment, and thus, they might be considered for bladder preservation therapy (trimodality therapy) with maximum TURBT, followed by combined chemoradiation. A multidisciplinary management model is resulted from high prevalence of systemic failure of MIBC patients. In this context, systemic therapy is important. Despite the use of primary surgical management to treat MIBC, which is based on radical cystectomy and pelvic lymph-node dissection, up to half of patients will obtain tumors at distant sites in the end due to the presence of pre-existing disseminated occult micrometastases (3,4), and for these individuals, perioperative platinum-based chemotherapy (PBCT) comprises the standard of care (5). Despite such aggressive treatment options, the survival rate of advanced or metastatic patients is low; moreover, until recently, prognosis is not changed significantly. Thus, it is essential to combine local and systemic therapies to improve outcomes (6).

Immunotherapy has been used to treat bladder cancer for several decades. So far, Intravesical Bacillus Calmette-Guérin (BCG) is the best effective intra-vesicle drug for NMIBC (7).

However, there is a limit to the treatment of bladder cancer. For disease progression and resistance to PBCT, there is only one intermediate treatment option that is valid and recently approved by the European Drug Administration. However, therapeutic modalities included cancer vaccines, immune checkpoint inhibitors (ICPIs) and immunogenic therapy are emerging as alternative immunotherapy for various bladder cancer patients. Several drugs have recently been approved by the Food and Drug Administration (FDA) for advanced and metastatic bladder cancer as a secondary systemic treatment or primary treatment for patients who are unsuitable for PBCT. We summarize the current state of immunotherapies and advances in the chemotherapy landscape for perioperative MIBC treatment. Moreover, we critically review topics that require further development, limitations, and future perspectives in this field.

Cancer immunology

The immune system has two functions in carcinogenesis, specifically, the elimination of cancer cells and facilitating the growth and spread of disease via immune evasion (8). Based on the theory of immunoediting, the host immune

system attacks a colony of cancer cells, facilitating their elimination. Tumor-specific mutations can result in neoantigens that are targeted by the immune system, and these differentiate non-self from self (9). CD8⁺ cytotoxic T cells are thought to mediate tumor regression, as they realize and specifically target cancer cells which have tumor-specific antigens on surface including somatic neoantigens (10). Tumor cell recognition by this population is associated with exhaustion owing to interactions with inhibitory receptor ligands presented by tumor, such as programmed death-receptor 1 (PD-1) and programmed death-receptor ligand 1 (PD-L1). Moreover, CD8⁺ cytotoxic T-cell activation is accompanied by CD4⁺ regulatory T cell (Treg) accumulation, which results in the suppression of effector T cell function (11). These adaptive immune pathways and associated factors such as ligands, receptors and mediators comprise the primary potential targets of immunotherapy. T cell response frequency and potency, dictating immunotherapy efficacy, are particularly modulated by co-stimulatory and co-inhibitory molecules, and these can be further modified by external stimuli (12). Antibody-based checkpoint blocks up immunotherapy largely functions by upswing the immune system to target tumor cells. There is various mechanism, for instance anti-cytotoxic T lymphocyte-associated protein-4 (CTLA-4) seems to primarily exert its physiologic effects by affecting major CD4⁺ T cell subsets, specifically modulating helper T cell (Th) activity, promoting effector T cells and suppressing Treg immunosuppressive functions. Immune checkpoint factors that are PD-1, PD-L1 and CTLA-4 comprise novel targets for immunotherapy, which is based on their co-inhibitory signals that affect T cell functions with respect to normal host cells, which can be imitated by cancer cells (13). Overall, tumor antigens cause tumor-specific immune reactions in various pathway; moreover, some antigens do not inevitably occur tumor rejection. Therefore, cancer may vary with regard to sensitivity and response to immunotherapy. On the other hand, this is still widely used NMIBC treatment modality; further, it has a more important role in treatment settings for advanced bladder cancer. In addition, there are reports from the “The Cancer Genome Atlas” Project (TCGA) indicates that there are three subtypes of MIBC based on mutations and deletion at regions of DNA amplification (14). Bladder cancer is concerned with many different mutations, highlighting its potential susceptibility to immunotherapy, based on recognizable antigen variability, although the concordance between these TCGA-based subtypes and transcriptional

subtypes is not currently clear (14).

Neoadjuvant chemotherapy (NACT) in MIBC

Several randomized controlled trials (RCTs) and meta-analyses have investigated the contribution of NACT, administered before radical cystectomy, to improving survival. One meta-analysis reported that cisplatin-based combination NACT can result in a 16% reduction in overall risk of death, compared to that with locoregional therapy alone. When considering only regimens comprising cisplatin/carboplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)-like chemotherapy, NACT is related to even better survival [hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.74–0.91] with an absolute 5-year survival benefit of 8% (15). In these studies, PBCT was used, and the results are not suitable for supporting non-cisplatin-based therapy in the neoadjuvant environment. Some adjuvant studies also showed similar efficacy with a gemcitabine-cisplatin combination, which is less toxic and has been expanded to a neoadjuvant setting (16).

Thus, in MIBC patients (and particularly those with clinical > T3 disease), NACT should be administered if a platinum-based regimen can be tolerated by the patient. If it cannot be tolerated or in the case of resistance, patients should proceed directly to radical cystectomy. Although cisplatin-based NACT is associated with pathologic downstaging and an overall survival (OS) benefit, more than 40% of patients diagnosed with urothelial carcinoma remain ineligible for cisplatin-based chemotherapy (17,18). Ineligibility is most often secondary to impaired renal function but poor performance status, hearing loss, peripheral neuropathy, and heart failure are also criteria used to exclude cisplatin therapy (18). Even in those patients eligible to receive cisplatin, a meta-analysis of 13 trials including 886 patients found that the pathologic complete response rate for those receiving neoadjuvant cisplatin-based chemotherapy was only 28.6% (19).

Overall, bladder cancers exhibit a mutational spectrum highly enriched in mutations in chromatin regulatory genes (14). Differences in mutation patterns suggest that different oncogenic mechanisms might be present. Moreover, this suggests new targets for bladder cancer treatment. Level I evidence suggests PBCT use in the neoadjuvant setting (NACT) for MIBC patients prior to radical cystectomy, which is associated with improved OS (median survival 76 vs. 44 months in the intention-to-treat population) and optimal results for those exhibiting complete pathological

response to therapy (20). However, trials investigating the use and efficacy of adjuvant PBCT for patients with advanced disease have encountered different challenges with respect to patient recruitment, design, and the necessity of subsequent therapies. Despite this, because effective salvage therapies are lacking, many experts suggest that patients at a high risk of relapse (pT3/4 and/or pN+) should be treated with adjuvant PBCT if neoadjuvant PBCT was not previously used. Despite aggressive multimodal therapy comprising NACT and radical surgery, many patients with MIBC experience disease recurrence and subsequently succumb to their disease. Therefore, there is a pressing need for alternative or additional treatments for this population. In addition to concerns related to potential toxicity, such approaches are perceived to offer marginal benefits and it has been suggested that additional treatment is not required for those with organ-confined disease, resulting in their lack of utilization. A recent exploration of urothelial carcinoma biomarkers also led to the identification of predictive mutations that could help to select patients who are most likely to benefit from neoadjuvant therapy.

Immunotherapy in MIBC

As stated, in addition to potential toxicity concerns, these neoadjuvant therapies are not used due to their perceived relatively low benefit and concerns that additional treatment is not required for patients with organ-confined disease. Therefore, alternative or additional treatments are needed for these individuals. Currently, several immunotherapeutic drugs that inhibit immune checkpoints such as PD-1 (nivolumab/pembrolizumab), PD-L1 (durvalumab/avelumab), and CTLA-4 (ipilimumab/tremelimumab) have been tested and/or are used clinically for various types of cancer including urothelial carcinoma. Among these, five (atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab) agents have been approved by the US Food and Drug Administration (USFDA); efforts are also being made to investigate the efficacy of immunotherapy, especially with checkpoint inhibitors (CPIs) for MIBC. Whereas results are not available with respect to the efficacy of CPIs for patients with MIBC based on the use of neoadjuvant or adjuvant therapy, currently, different active trials are recruiting patients and are ongoing (*Table 1*).

Immunotherapy in the neoadjuvant setting

In the ABACUS phase II trial (NCT02662309), patients

Table 1 Neoadjuvant immunotherapy-related clinical trials on muscle-invasive bladder cancer

Disease setting	Clinical trial number	Drug(s) investigated	Disease state	Phase	Primary endpoint
Neoadjuvant	NCT02662309 (ABACUS)	Atezolizumab	Neoadjuvant in MIBC	II	Pathological complete response
Neoadjuvant	NCT02451423	2x3 weekly cycles of atezolizumab (one infusion on the first day of each cycle) prior to cystectomy surgery	Neoadjuvant in MIBC	II	Pathological complete response and immune parameters
Neoadjuvant	NCT02845323	Nivolumab + urelumab versus nivolumab	Neoadjuvant in MIBC with cisplatin-ineligible patients	II	Immune response of tumor infiltrating CD8 ⁺ T cell density
Neoadjuvant	NCT02812420	Tremelimumab + durvalumab	Durvalumab and tremelimumab for the treatment of patients with muscle-invasive, high-risk urothelial cancer that cannot be treated with cisplatin-based therapy before surgery	I	Safety/toxicity
Neoadjuvant	NCT02736266	Pembrolizumab	MIBC, were scheduled for RC, and had a clinical (c) T2–4aN0M0 stage	II	Pathological complete response
Neoadjuvant	NCT02690558	Pembrolizumab + gemcitabine/ cisplatin versus placebo + gemcitabine/cisplatin	Neoadjuvant in MIBC	II	Pathological downstaging to < pT2 defined as pT0–T1N0M0 at the time of cystectomy
Neoadjuvant	NCT02365766	Pembrolizumab + gemcitabine/ cisplatin (cisplatin-eligible) or gemcitabine (cisplatin-ineligible)	Neoadjuvant in MIBC	Ib/II	Safety/toxicity
Neoadjuvant	NCT02989584	Atezolizumab + gemcitabine/ cisplatin	Metastatic and MIBC	I/II	Safety/toxicity
Neoadjuvant	NCT03549715	ddMVAC + durvalumab (D) alone or in combination with tremelimumab	Neoadjuvant in MIBC	II	Pathological complete response

MIBC, muscle invasive bladder cancer; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin.

with MIBC (T2–T4a) who were candidates for cystectomy but considered cisplatin-ineligible received two cycles of neoadjuvant atezolizumab. Primary outcomes addressed in this study were efficacy, based on pathological complete response (pCR), and also safety, relapse-free survival, and biomarker analysis. This study achieved its primary endpoint with a pCR rate of 31% (27/88; 95% CI: 21–41%) (21). Moreover, through dual staining for CD8 and granzyme B (GZMB), which is an essential effector for lymphocyte activity and an alternate marker of activated CD8⁺ cells, these markers were found to be expressed in responding tumors associated with an inflamed phenotype (14 of 16, 88%); this was in contrast to that in relapsing inflamed tumors, which were found to harbor low levels of CD8⁺ and GZMB⁺ cells (3 of 10, 30%; $P < 0.05$) (21). This

suggests that preexisting T cell immunity could underlie the unexpectedly high response rates in the neoadjuvant setting. Further, the immune infiltrate quality, aside from CD8 expression, is relevant to the outcome. This reversal in biomarker significance suggests that the utility of these markers in association with anti-PD-L1 treatment depends on the clinical setting of urothelial carcinoma. Moreover, TCGA data with gene expression and DNA analysis data in this study indicated changes in urothelial carcinoma biology with more advanced disease. We thus speculate that approaches based on different treatments and biomarkers are needed to optimize outcomes in diverse clinical settings. The biomarkers identified in those studies, and especially those based on post-treatment tissue, could aid in patient selection and provide an improved understanding of disease

biology.

A phase II trial of neoadjuvant atezolizumab administration based on 1,200 mg for one, two, and three doses before cystectomy will give significant information regarding the effects of and requirement for multiple CPI applications (NCT02451423). In this multi-dose portion trial, patients with adverse pathology (pT3/pT4 or N+) at the time of cystectomy and no metastatic disease will be permitted to receive adjuvant atezolizumab for up to 16 cumulative doses. For NACT-ineligible patients, but fit to undergo surgical resection of their cancer by cystectomy, a combination phase II trial is underway comprising two nivolumab cycles, an antibody targeting PD-1 to reactivate T cells, plus urelumab, an CD137-agonistic antibody with additional activating properties, will be compared to two cycles of nivolumab alone (NCT02845323). In addition, a pilot presurgical study will evaluate durvalumab (a PD-L1 inhibitor) and tremelimumab (a CTLA-4 inhibitor) safety; for this, 28 patients are enrolled. This will determine if this is an effective and safe neoadjuvant therapy for MIBC patients who are not eligible for cisplatin-based therapy (NCT02812420) (22).

Pembrolizumab before cystectomy was also investigated in the PURE01 study (NCT02736266), with the selected patients exhibiting predominant variant histologies (usually defined by >50% of this component within the tumor specimen) (23). In this trial, 21 patients achieved pCR (42%, 95% CI, 28–57%) and 27 patients experienced pathologic downstaging to < pT2 (54%, 95% CI, 39–68%) (23). The significant differences in tumor responses, which appeared to be mainly dependent on tumor biomarkers instead of histological features, suggest that revised inclusion criteria should consider squamous-cell carcinoma histologies and all patients with rare biological features that lead to outstanding responses.

Another phase II trial investigated a combination comprising four cycles of pembrolizumab with four cycles of gemcitabine/cisplatin prior to cystectomy (NCT02690558); this will address the pressing question of the additive benefit of immunotherapy in addition to PBCT (23). Pembrolizumab response was found to be dependent on tumor PD-L1 status. Moreover, the primary pT0 endpoint was realized for 54.3% of patients harboring PD-L1-positive tumors, which was defined based on a combined positive score (CPS) comprising PD-L1 expression on both immune and tumor cells (CPS \geq 10 in 35 patients); however, the authors only observed a pCR in 13.3% of patients with CPS <10 (n=15). Moreover, tumor mutational

burden scores of \geq 15 mutations/Mb in pretreatment tumors were associated with high pT0 frequencies (23). Another trial (NCT02365766) will address the effect of cisplatin combined with pembrolizumab and gemcitabine prior to cystectomy and will include cisplatin-eligible and ineligible.

Adjuvant immunotherapy

Several trials are currently investigating the use of ICPIs in an adjuvant setting, in which the evidence of PBCT benefit is much lower than that in the neoadjuvant setting (5). In general, the eligibility criteria for these studies include the following: patients who received NACT with at least pT2 or node-positive disease at cystectomy; cisplatin-ineligible patients with at least pT3 or node-positive disease at cystectomy; patients who decline adjuvant cisplatin-based chemotherapy with at least pT3 or node-positive disease at cystectomy. There are also three adjuvant ICPI clinical trials currently underway (Table 2), specifically a randomized phase III trial of pembrolizumab versus observation for patients with locally-advanced bladder cancer post-cystectomy (NCT03244384). For high-risk MIBC patients unqualified cisplatin-based chemotherapy or with persistent muscle-invasive disease despite the use of NACT, pembrolizumab administered post-cystectomy will improve OS and disease-free survival (24).

In another randomized phase III adjuvant study, 700 patients harboring PD-L1-positive high-risk urothelial carcinomas (muscle-invasive urothelial carcinoma of the bladder, renal pelvis, ureter after surgical resection without prior PBCT) will be recruited and randomized in a 1:1 manner to receive atezolizumab at 16 doses for 1 year versus observation (NCT02450331). In another trial, a randomized phase III study will explore adjuvant nivolumab with 640 patients based on the same setting compared to that in the previous trial; however, whereas biomarker analysis of cystectomy specimens will obviously be performed, no specific biomarker level is required for entry to the study (NCT02632409).

Several trials are also available for ineligible patients or those who refuse cystectomy. One is a phase II trial comprising pembrolizumab combined with gemcitabine and hypofractionated radiotherapy (52 Gy in 20 fractions) (NCT02621151), whereas the other is a phase II trial of pembrolizumab, cisplatin (weekly for 6 weeks), and radiotherapy (64 Gy in 32 fractions) after maximal TUR-BT (NCT02662062) to address the bladder-sparing space. These trials will be informative with respect to

Table 2 Adjuvant immunotherapy-related clinical trials on muscle-invasive bladder cancer

Disease setting	Clinical trial number	Drug(s) investigated	Disease state	Phase	Primary endpoint
Adjuvant	NCT02632409	High-risk MIBC after surgical resection	Nivolumab versus placebo	III	DFS
Adjuvant	NCT02450331	High-risk MIBC after surgical resection	Atezolizumab versus observation	III	DFS
Adjuvant	NCT03244384	High-risk MIBC after surgical resection	Pembrolizumab versus observation	III	OS, DFS
Adjuvant	NCT02662062	After maximally resected MIBC	Pembrolizumab and cisplatin and radiotherapy	II	Safety/toxicity
Adjuvant	NCT02621151	MIBC with patients who are not candidates for or decline radical cystectomy	Pembrolizumab and transurethral resection of bladder tumor and gemcitabine and external beam radiation therapy	II	DFS
Adjuvant	NCT02891161	MIBC (T2–4N0–2M0) of the bladder	Combining durvalumab with RT followed by adjuvant durvalumab	Ib/II	Safety/toxicity PFS, DCR

MIBC, muscle invasive bladder cancer; DFS, disease free survival; RT, radiotherapy; OS, overall survival; PFS, progression-free survival; DCR, disease control rate.

the effect of radiation on antigen release, production of immune cell infiltrates, and immune activity based on blood parameters; in addition, re-TURBT samples will be accessible. Further, in a phase Ib study, durvalumab combined with 64.8 Gy administered to the bladder will be explored for unresectable and cystectomy-ineligible patients (NCT02891161).

Discussion

Perioperative treatment strategies include therapies administered immediately before or after surgery. Theoretically, chemotherapy delivery prior to (neoadjuvant) or after (adjuvant) definitive local therapy should be as efficacious with respect to the elimination of micrometastases. Further, preliminary surgery could result in pathological confirmation of disease extent before systemic therapy. Moreover, 6–15% of patients with MIBC reportedly achieve pCR with TURBT alone, and these patients have exceptional outcomes without chemotherapy (3,20). Thus, the use factors related with recurrence risk to improve patient selection for treatments, thereby preventing overtreatment or undertreatment, represent a clear benefit of adjuvant strategies rather than neoadjuvant approaches. However, in practice, many MIBC patients who select preliminary surgery never receive adjuvant chemotherapy. Bladder cancer is primarily a disease

affecting the elderly, as the median age at diagnosis is 73 years; accordingly, radical cystectomy results in marked morbidity. For example, a retrospective study based on 1,142 consecutive patients subjected to radical cystectomy indicated that 30% experienced grade 2–5 complications within 90 days of surgery, which could effectively delay the administration of effective adjuvant chemotherapy (25). Thus, perioperative therapy timing might be more critical for patients with MIBC, and the proportion of MIBC patients receiving chemotherapy might be increased based on the use of a neoadjuvant, rather than adjuvant, approach. However, neoadjuvant cisplatin-based chemotherapies are still underutilized for bladder cancer management, even based on a current cohort at a high-volume tertiary center. It also seems that adjuvant cisplatin-based chemotherapy is underutilized, even for patients with a high risk of recurrence. The landscape of bladder cancer treatment has evolved rapidly with the introduction of ICPIs for patients with advanced disease, and clinical trials are underway to evaluate a potential role for these drugs in earlier disease states including NMIBC and MIBC. ICPIs are associated with long-term durable responses and good safety profiles based on a number of clinical trials. However, approximately 70–80% of patients might not respond to such agents. Therefore, more research, based on the combination of ICPI therapy and other therapeutic modalities like cytotoxic chemotherapy or different therapeutic targets, is required

to strengthen the effects of immunotherapies. Promising preliminary data for immune checkpoint inhibition in the neoadjuvant setting will hopefully lead to the expansion of perioperative chemotherapy to include those patients ineligible for cisplatin-based therapy, in addition to leading to better pathologic responses with associated improvements in survival outcomes. Currently, additional compounds and combinations are being tested based on different clinical situations in many clinical trials. However, overall response rates can be improved and thus, additional efforts must be made to optimize utility, while controlling side effects. This will include future research on biomarkers to accurately predict and optimize treatment success, as well as economic factors.

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Footnote

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References

1. Antoni S, Ferlay J, Soerjomataram I, et al. Bladder cancer incidence and mortality: A global overview and recent Trends. *Eur Urol* 2017;71:96-108.
2. Nielsen ME, Smith AB, Meyer AM, et al. Trends in stage-specific incidence rates for urothelial carcinoma of the bladder in the United States: 1988 to 2006. *Cancer* 2014;120:86-95.
3. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666-75.
4. Yafi FA, Aprikian AG, Chin JL, et al. Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. *BJU Int* 2011;108:539-45.
5. Alfred Witjes J, Lebre T, Comperat EM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2017;71:462-75.
6. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer* 2011;117:276-82.
7. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol* 2017;197:S142-5.
8. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;3:991-8.
9. Desrichard A, Snyder A, Chan TA. Cancer neoantigens and applications for immunotherapy. *Clin Cancer Res* 2016;22:807-12.
10. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. *Nat Rev Immunol* 2012;12:269-81.
11. Thomas DA, Massague J. TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. *Cancer Cell* 2005;8:369-80.
12. Driessens G, Kline J, Gajewski TF. Costimulatory and coinhibitory receptors in anti-tumor immunity. *Immunol Rev* 2009;229:126-44.
13. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013;39:1-10.
14. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* 2014;507:315-22.

15. Yin M, Joshi M, Meijer RP, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: A systematic review and two-step meta-analysis. *Oncologist* 2016;21:708-15.
16. Yuh BE, Ruel N, Wilson TG, et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. *J Urol* 2013;189:1682-6.
17. Hussain SA, Palmer DH, Lloyd B, et al. A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. *Oncol Lett* 2012;3:855-9.
18. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. *J Clin Oncol* 2011;29:2432-8.
19. Petrelli F, Coinu A, Cabiddu M, et al. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol* 2014;65:350-7.
20. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-66.
21. Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nat Med* 2019;25:1706-14.
22. Gao J, Siefker-Radtke AO, Navai N, et al. A pilot presurgical study evaluating anti-PD-L1 durvalumab (durva) plus anti-CTLA-4 tremelimumab (treme) in patients (pts) with high-risk muscle-invasive bladder carcinoma (MIBC) who are ineligible for cisplatin-based neoadjuvant chemotherapy (NAC). *J Clin Oncol* 2019;37:4551.
23. Necchi A, Raggi D, Gallina A, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. *Eur Urol* 2019. [Epub ahead of print].
24. Apolo AB, Rosenberg JE, Kim WY, et al. Alliance A031501: Phase III randomized adjuvant study of MK-3475 (pembrolizumab) in muscle-invasive and locally advanced urothelial carcinoma (MIBC) (AMBASSADOR) versus observation. *J Clin Oncol* 2020;77:439-46.
25. Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. *Eur Urol* 2009;55:177-85.

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