



## Update on the Targeted Therapy of the Bladder Cancer

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### Abstract

Bladder cancer was considered as immunogenic cancer many years ago since the detected response to BCG instillation in the bladder. Recently, utilization of check point inhibitors in malignancies is the new era in cancer immunotherapy. This novel treatment is now approved for melanomas, however in bladder cancer still in the starting phase with promising results. Many trials have been started to investigate the role of check point inhibitors in non-muscle invasive and in metastatic bladder cancer. Many efforts at the pre-clinical level suggested a role for steroid hormones in bladder cancer pathogenesis, however no available prospective data on the role of hormonal therapy in bladder cancer. In this short review we present the updates on checkpoint inhibitors in the bladder cancer and the suggested role for hormonal therapy in the future.

**Keywords:** Bladder cancer; Checkpoint inhibitors; Atezolizumab; Hormonal therapy; CTLA-4

### Introduction

Bladder cancer (BC) is one of the aggressive tumors worldwide, and represents the 4<sup>th</sup> cause of cancer mortality in USA [1]. About 75% of patients present with non-muscle invasive disease (NMIBC) [2]. For these patients, transurethral resection of the bladder tumor is the main used treatment [3]. The other 25% of the patients have muscle invasive disease (MIBC) at the time of the first diagnosis [2]. Generally, the survival outcomes after treatment of BC are not satisfying. Indeed, no improvement regarding the outcomes could be achieved in the last decades [3]. Up to 60% of NMIBC patients may develop recurrence after been cured from BC [4]. For MIBC, in which Radical Cystectomy (RC) is still the gold standard treatment, the overall survival after this operation is 50% [5].

Currently, the ability of the malignant cells to evade the destruction by the immune system is one of the cancer hallmarks [6]. Previously, BC immune-reactivity was early established after introduction of Bacille-Calmette-Guerin (BCG) in the treatment of BC [7]. Immunotherapy using Check Point Inhibitors (CPI) is now a new era in cancer treatment. After approval of CPI in melanomas [8], trials were expanded to other malignancies, with promising initial results in urological tumors [9,10].

BC displayed higher incidence in males than in females regardless the exposure to the risk factors [11-13]. Furthermore, females displayed worse outcome than males based only on gender difference [14]. Based on this gender related difference, hormonal characteristics of the BC have been investigated and displayed some evidence of androgen and estrogen roles in BC pathogenesis [15]. In this manuscript, we provide an updated overview on the targeted therapy of the BC and the possibility to improve the current unpleasant outcome.

### Immunotherapy

Normally immune system is under control of stimulatory and inhibitory signals to avoid autoimmune destructive activity [16]. Inhibition of these inhibitory signals to maximize the anti-tumor T-cell mediated immunity is the most recent strategy has been utilized in cancer immunotherapy [17]. Two types of CPI are in current use to inhibit the inhibitory signals of immune system.

### Anti-PD-1/PD-L1

Programmed Death-1 (PD-1) is widely expressed on immune cells including T- cells and Natural Killer cells (NK). The main role of PD-1 is to limit the activity of immune system in the peripheral tissues [18]. Expression of PD-1 in urothelial cancer cells detected by immunohistochemistry and association with aggressive nature of BC was approved by some investigators [19]. This represented the rationale to investigate the inhibition of PD-1 at the clinical level in BC patients. Trials on PD-1

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inhibition in BC already started with promising preliminary results [20]. Based on the available literature, the most promising results for CPI in urothelial carcinoma were displayed by Atezolizumab (MPDL3280A). This drug was investigated in about 150 patients with metastatic BC [10]. Some correlation was detected between the PD-1 positivity on the tumor infiltrating leucocytes and the response rate. Furthermore, the overall response rate was significantly higher in patients with non-visceral metastasis in comparison to patients with visceral metastasis [10]. These initial results, however limited by small number of participants, suggest the affection of response by the metastatic burden. This also might be explained by better immune reactivity in patients with less tumor burden as CPI itself not improve the immune status directly, but only open the way to immune system to attack the malignant cells.

One of the challenges in CPI application is the identification of suitable patients who might get benefits from these expensive drugs. Factors that can affect immune status might affect the response to CPI; for example previous chemotherapy or radiotherapy. Clear understanding of the impact of these therapeutic modalities on the immune system is mandatory to optimize the usage of CPI in BC. Also a very recent study reported on genomic based response to CPI [21].

Anti-PD-1 displayed well tolerability. Fatigue and nausea were the main reported side effects for these drugs [22].

#### Anti-CTLA-4

Anti T-lymphocyte-associated antigen 4 (CTLA-4) is the other subgroup of CPI. Normally CTLA-4 can down regulate the immune activity through binding to B7 membrane protein of the antigen presenting cell (APC) [23]. This type of CPI is already investigated in prostate cancer [24]. Yet regarding BC, no clinical results were reported until now. Only it was tested for tolerability in localized BC patients by giving 2 doses before undergoing radical cystectomy [25] and displayed acceptable tolerability, however less than anti PD-1. Theoretically, this type of CPI was expected to improve the response of non-muscle invasive bladder cancer to BCG [26]. Indeed, a Phase I safety and efficacy clinical trial was launched to investigate the impact of combination of BCG instillation with MK-3475 in non-muscle invasive high risk BC (clinical trial NCT02324582).

#### Hormonal therapy

Is bladder cancer an endocrine sensitive tumor?

Until now, hormonal therapy has no role in the BC treatment, however it is expected to be investigated in the near future. Gender disparity in bladder cancer is clinically evident. Number of men diagnosed for BC is three to four times than affected females [27]. This was explained previously as smoking is more common in men than women. This difference between genders was detected also in smokers [28], which means that difference in exposure to smoking cannot explain this gender disparity. Despite lower incidence, women are presented with higher MIBC stages and have higher mortality than men [29,30]. This might suggest higher progression of BC in women. These clinical observations raised the question about the role of androgen and estrogens in the pathogenesis of BC [15]. A very recent meta-analysis on the Incidental Prostatic Cancer (IPC) in radical cystoprostatectomy specimens suggested that IPC is might be associated with more aggressive BC [31]. This might be explained on basis of androgen sensitivity may be enrolled in the pathogenesis of both prostatic and bladder cancers.

#### Clinical evidence on the role of hormonal therapy in BC

In a retrospective multi-center study, from 20328 BC patients 239 patients received Androgen Deprivation Therapy (ADT) for prostate cancer. These subgroup displayed significant lower recurrence rate of their BC than other patients (40% versus 76%,  $p < 0.001$ ) [32]. Tamoxifen was tested as a chemo-sensitizer in 30 patients with advanced BC with reported response rate of 58% [33].

#### Conclusion

Checkpoint inhibitors are suggested to have a role in treatment of bladder cancer. Proper selection of the candidate patients for this kind of treatment still the main challenge. Complete understanding of the genomic criteria of bladder cancer and the impact of chemotherapy and radiotherapy on immune system can help optimal application of checkpoint inhibitors. Hormonal therapy might have a role in the near future; however the endocrinal basis of bladder cancer still not completely clarified.

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