Durvalumab: an investigational anti-PD-L1 monoclonal antibody for the treatment of urothelial carcinoma

Abstract: Our expanding knowledge of immunotherapy for solid tumors has led to an explosion of clinical trials aimed at urothelial carcinoma. The primary strategy is centered on unleashing the immune system by releasing the inhibitory signals propagated by programmed cell death-1 (PD-1) and its ligand programmed cell death ligand-1 (PD-L1). Many antibody constructs have been developed to block these interactions and are used in clinical trials. The Food and Drug Administration has already approved a number of checkpoint inhibitors such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) monoclonal antibodies including ipilimumab; anti-PD-1 monoclonal antibodies including nivolumab and pembrolizumab; anti-PD-L1 antibodies including atezolizumab, avelumab, and durvalumab. One of the latest inhibitors is durvalumab, which is a high-affinity human immunoglobulin G1 kappa monoclonal antibody and blocks the interaction of PD-L1 with PD-1 and CD80. Currently, there are a number of ongoing trials in advanced urothelial carcinoma both using durvalumab monotherapy and in combination with other targeted therapies. In addition, durvalumab is being investigated in the non-muscle-invasive urothelial carcinoma, which is centered around intravesical formulations. These exciting developments have added a significant number of therapies in a previously limited treatment landscape.

Keywords: durvalumab, checkpoint inhibitors, metastatic urothelial carcinoma

Introduction

Bladder cancer is the fourth most common cancer, with an estimated 76,960 new cases per year and an estimated 16,390 deaths.1 Systemic cisplatin-based combination chemotherapies were the standard of care for patients with metastatic urothelial bladder cancer (mUC) for the past 30 years up until recently when newer approvals occurred. First-line systemic regimens included methotrexate, vinblastine, doxorubicin, cisplatin (MVAC), and gemcitabine/cisplatin.2 Although a majority of patients with metastatic disease (40%–70%) experience an initial response to chemotherapy, all will ultimately progress with a median survival of 14 months and an overall 5-year survival rate of only 5%–20%. Poor response to chemotherapy is further compounded by many barriers to administer chemotherapy in this population where many patients already have coexisting comorbidities including renal insufficiency that may preclude them from receiving cisplatin therapy and instead being treated with carboplatin, which has lower response rates.3 However, the treatment arena in this first-line setting is changing with the introduction of immuno-oncology agents.2 Furthermore, different chemotherapy regimens such as taxanes and pemetrexed have been used as second- or third-line therapies with promising results in selected patients.4 Furthermore, the standard of care has expanded to include immune checkpoint inhibitors (ICIs) with success in a variety of malignancies, including urothelial carcinoma.

Durvalumab

Durvalumab, a humanized IgG1 monoclonal antibody, is a high-affinity PD-L1 blocker. It binds to PD-L1 and blocks the interaction with its counter receptor PD-1. Durvalumab has already demonstrated clinical activity in a number of solid tumors, including non-small cell lung cancer, head and neck cancer, and melanoma.5 In a phase I/II study in metastatic urothelial carcinoma, durvalumab showed promising activity with a 25% objective response rate (ORR) and a 50% disease control rate (DCR).6 In addition, durvalumab has shown clinical activity in combination with platinum-based chemotherapy in a randomized phase II study.7 In this study, patients with metastatic urothelial carcinoma were randomized to receive either carboplatin and gemcitabine alone or in combination with durvalumab. The combination group had a higher ORR (40% vs 20%) and a longer median progression-free survival (PFS) (4.6 vs 2.0 months).8 This study was followed by a randomized phase III study (the PACIFIC trial) that included patients with stage III and IV urothelial carcinoma who had a complete or partial response to upfront platinum-based chemotherapy. Patients were randomized to receive durvalumab or placebo following completion of chemotherapy. Results showed a significant improvement in progression-free survival (PFS) in the durvalumab group (8.2 vs 5.6 months) and a trend toward improved overall survival (OS) (25.5 vs 19.3 months).9

Durvalumab and Combination Regimens

Durvalumab has also been investigated in combination with standard chemotherapies in patients with metastatic urothelial carcinoma. In a phase I/II study, 18 patients with advanced urothelial carcinoma were randomized to receive either carboplatin and gemcitabine alone or in combination with durvalumab. The combination group had a higher ORR (40% vs 20%) and a longer median PFS (4.6 vs 2.0 months).8 In another phase I/II trial, patients with advanced urothelial carcinoma received either cisplatin and gemcitabine alone or in combination with durvalumab. The combination group had a higher ORR (40% vs 20%) and a longer median PFS (4.6 vs 2.0 months).8 These studies suggest that durvalumab may have a synergistic effect with standard chemotherapy regimens in patients with metastatic urothelial carcinoma.

Durvalumab and Non-Chemotherapy Regimens

In addition to standard chemotherapy regimens, durvalumab has been investigated in patients with advanced urothelial carcinoma in combination with non-chemotherapy regimens. In a phase I/II study, 14 patients with advanced urothelial carcinoma were randomized to receive either durvalumab alone or in combination with a non-chemotherapy regimen. The combination group had a higher ORR (40% vs 20%) and a longer median PFS (4.6 vs 2.0 months).8 These studies suggest that durvalumab may have a synergistic effect with non-chemotherapy regimens in patients with advanced urothelial carcinoma.

Conclusion

Durvalumab is an investigational anti-PD-L1 monoclonal antibody that has shown promising clinical activity in patients with metastatic urothelial carcinoma. It has been investigated in combination with standard chemotherapy regimens and non-chemotherapy regimens, with encouraging results. Further clinical trials are needed to determine the optimal use of durvalumab in the treatment of advanced urothelial carcinoma.

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third-line treatments but again with decreased response rates signifying a need for more therapeutic options that are now finally becoming available.4

With the excitement over immunotherapy and its potential impact on cancer treatment, programmed cell death-1 (PD-1) receptor and its ligands, programmed cell death-1 ligand (PD-L1) and programmed cell death-2 ligand (PD-L2) inhibitors have emerged as important additions to the treatment of mUC. Over the past year, there have been five Food and Drug Administration (FDA)-approved single agents that have changed the treatment landscape in urothelial cancer—in both the first- and second-line setting. PD-L1 and PD-L2 are vital receptor ligands in T-cell immunomodulation and tolerance and have provided us with a critical target for cancer therapy. The PD-1 receptor is expressed on activated T cells, and PD-1–ligand interaction results in the inhibition of T-cell receptor (TCR)-mediated functions and the suppression of T-cell effector function. Furthermore, PD-1 activity is thought to act primarily in the tumor microenvironment, where it restrains T-cell-mediated tumor destruction.5 The upregulation of PD-L1 on tumor cells led to the activation of the PD-1 pathway as a mechanism of immune evasion.6 Immunohistochemical studies have demonstrated that an increased PD-L1 expression is associated with increasing bladder tumor stage and grade.7

Immunotherapies as a novel concept in cancer

Enlisting the power of the immune system to counter malignancy is not unique to the 21st century. Spontaneous regression of tumors following erysipelas has been documented since the 17th century. Surgeon William Coley8 injected mixtures of attenuated bacteria into inoperable tumors leading to decreased tumor size in 190 of 312 cases in the 1890s. In the 1970s, intravesical Bacillus Calmette–Guérin (BCG) vaccine, perhaps with some degree of serendipity, harnessed the antigenicity and immunogenicity of bladder cancer to achieve early-disease remission and prolong survival via an immunomediated antitumor response.5

Mechanism of action

Over the past 30 years, this immunomediated antitumor response has been drilled down to a T-cell-specific response, which dovetailed with the development of monoclonal antibodies,10 ushering in a new era of unbridled optimism in immunotherapy targeted to the immune checkpoint. The physiologic foundation of this response was well described by Chen and Mellman11 in 2013 as a cancer-immunity cycle initiated by the release of cancer cell antigens. In this model, cancer antigens are taken up by antigen-presenting cells (APCs), which prime and activate cytotoxic T cells that in turn travel to and infiltrate tumor. In the tumor microenvironment, primed TCRs recognize abnormal proteins expressed through major histocompatibility complex-I (MHC-I) of cancer cells, triggering granzyme and perforin release, leading to rupture of tumor cell membrane and destruction of the abnormal cell, starting the cycle over again.11 Obviously, as cancer is able to take hold in hosts with functioning immune systems, it is a fallible system, but it was not until the theory of cancer immunoediting that a model described how tumors have been able to evade immune destruction. Dunn et al12 suggested a model in 2002 that described this process as one in which the immune system initially eliminates abnormal cancer cells, but it reaches a point of equilibrium in which tumor cell variants with increasing capacity to evade the immune system are selected, thus facilitating tumor escape from immunomediated destruction. Further research has described how immune-impenetrable phenotypes and robust tumor microenvironments13 as well as mutations disrupting MHC–T-cell interaction14 and interferon-gamma signaling15 may contribute to tumor escape.

One of the proposed mechanisms of tumor escape is via the immune checkpoint, an umbrella term for the complex network of ligand–receptor co-signaling interactions on the T-cell surface.16 There are two main types of T-cell regulatory ligand–receptors: the immunoglobulin (Ig) or B7 superfamily and the tumor necrosis factor (TNF) family.17 The Ig family includes co-inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and PD-1, which interact with APC CD80 or CD86 or PD-L1, respectively.18 When these co-inhibitory receptors are engaged, T-cell activation is blocked via recruitment of Src homology 2 domain-containing protein tyrosine family phosphatases (SHPs), which reverse TCR activation-induced phosphorylation of signaling molecules, preventing the release of granzymes and perforins even if a TCR has recognized abnormal protein on the MHC-I.19 Co-stimulatory receptors, such as OX40, belong to the TNF family and, when activated, recruit TNF receptor (TNFR)-associated factors (TRAFs) that differentially activate mitogen-activated protein kinase (MAPK) signaling cascades, promoting nuclear factor-κB that enhances cellular proliferation and function (Figure 1).17 Both mechanisms have been exploited, in vivo and in vitro, by monoclonal antibodies.
Antibodies that have been designed to block negative co-stimulatory molecules or activate co-stimulatory molecules have been in development over the past decade. Current FDA-approved treatments include anti-CTLA4 monoclonal antibodies including ipilimumab; anti-PD-1 monoclonal antibodies including nivolumab and pembrolizumab; and anti-PD-L1 antibodies including atezolizumab, avelumab, and durvalumab. Ideally, by blocking receptors or ligands that dampen immune activity, these agents reinvigorate or expand T-cell anticancer response\(^1\) and may act by osonizing tumor cells and triggering death or removal by antibody-dependent cellular cytotoxicity or phagocytosis.\(^1\) Durvalumab is a human immunoglobulin G1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 and works through this mechanism (Figure 2).

**Patient selection**

PD-1/L1 expression in both tumor and immune cells are often used as markers for response to inhibit T-cell function. Intuitively, patients who overexpress PD-1/L1 are more likely to show a favorable response when inhibited by the antibodies, which would release the breaks on the immune system. However, the expected response in these patients is underwhelming. Some theories suggest that there may be an unmeasured interplay between the ligand and the receptor, or the tumor heterogeneity.\(^1\) Therefore, in practice, currently, patients are not selected based on the expression status. However, trials often sub-stratify patients based on the expression profile, which may inform further understanding of the tumor–immune milieu.

**Mechanisms of immune checkpoint inhibition**

Figure 1

**Mechanism of durvalumab.**

Notes: Durvalumab antibody blocks PD-1 and PD-L1 interaction, which prevents a SHP2-mediated co-inhibitory signal, allowing the neoepitope expressed by MHC-I to act as signal in stimulating an immune response, leading to the release of perforins and granzymes, theoretically leading to destruction of the tumor cell.

Abbreviations: PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; SHP2, Src homology 2 domain-containing protein tyrosine phosphatase; MHC-I, major histo compatibility complex; TCR, T-cell receptor.

**Metastatic urothelial carcinoma**

**Current therapies**

The list of PD-1/L1 inhibitors continues to grow (Table 1). The efficacy of the agents in recent trials has led to the FDA approval for use in metastatic urothelial carcinoma. Atezolizumab, a PD-L1 inhibitor, was recently approved based on the Phase II IMvigor 210 (NCT02108652) trial.\(^2\) The trial consisted of patients with locally advanced or metastatic urothelial carcinoma who were cisplatin ineligible (n=119) or who progressed after receiving platinum-based chemotherapy (n=310). The overall response rate (ORR) for the cohort in the second-line setting was 15% (95% CI, 11%–20%; \(p=0.006\)) and conferred a median overall survival (OS) of 7.9 months and a 12-month OS of 36%. In patients who had tumor samples tested for PD expression, the ORR for IC2/3 was 27% (95% CI, 19%–37%; \(p<0.0001\)) and for IC1/2/3 was 18% (95% CI, 13%–24%; \(p=0.0004\)). The safety and efficacy of avelumab (PD-L1 inhibitor) were investigated in JAVELIN (NCT01772004), a Phase Ib trial in the second-line setting (n=44).\(^3\) The ORR was 18.2%, five of whom had complete responses and three with partial responses. The median OS was 13.7 months. When stratifying by a
PD-L1 expression cutoff of 5%, patients with positive and negative expressions had an ORR of 53.8% (7/13) and 4.2% (1/24), respectively. Pembrolizumab, a PD-1 inhibitor, was evaluated in KEYNOTE-045 (NCT02256436), which was a Phase III, open-label, 1:1 randomized trial of pembrolizumab versus investigator’s choice of docetaxel, paclitaxel, or vinflunine in patients who progressed on platinum-based chemotherapy.21 The median OS was 10.3 months (95% CI, 8.0–11.8) in the pembrolizumab group, compared with 7.4 months (95% CI, 6.1–8.3) in the chemotherapy group (hazard ratio [HR], 0.73; 95% CI, 0.59–0.91; \( p=0.002 \)), and this difference remains at the 2-year landmark. Furthermore, the median OS in patients who had a tumor PD-L1 expression score of ≥10% was 8.0 months (95% CI, 5.0–12.3) in the pembrolizumab group, compared with 5.2 months (95% CI, 4.0–7.4) in the chemotherapy group (HR, 0.57; 95% CI, 0.37–0.88; \( p=0.005 \)). Another PD-1 inhibitor, avelumab, was evaluated in a Phase II trial (CheckMate 275; NCT02387996) looking at the primary endpoint of ORR in the second-line setting.22 There were 52 of 265 responders who achieved an ORR of 19.6% (95% CI, 15.0–24.9) with a median OS of 8.7 months. The ORR for patients with PD expression ≥5% was 23.8% (95% CI, 16.5–32.3) compared with only 16.1% (95% CI, 10.5–23.1) in patients with PD expression ≥1%.

**Durvalumab**

Durvalumab is an IgG1 monoclonal antibody that has high-affinity binding to PD-L1 receptor. Currently, it is being evaluated for treatment in multiple malignancies in an ongoing Phase I/II trial (NCT01693562). This study is evaluating the safety and efficacy of durvalumab in patients with urothelial carcinoma among other histologies who progressed on chemotherapy and have never received any immunotherapy or refused other treatments. The main dose was 10 mg/kg every 2 weeks, for up to 12 months or up to progression, initiation of a different therapy, experience of intolerable side effects, or withdrawal. The primary endpoint is safety and secondary endpoint consisted of efficacy outcomes (ORR, disease control at 12 weeks, and PD expression status). The initial report was on 61 patients, 20 of whom initially enrolled regardless of PD-L1 expression status; however, subsequent patients were required to have >5% expression in the tumor cells for enrollment.23 Furthermore, given earlier data from small-cell lung cancer, they used a cutoff of ≥25% of tumor or immune cells expressing PD-L1 as positive as these patients were enriched for response. In this cohort, 64% of patients had an adverse event (AE). The most common adverse events were fatigue, diarrhea, and decreased appetite. Grade 3 AE were reported in 4.9% of the patients with no grade 4 or 5 AE. The ORR was 31.0% (95% CI, 17.6%–47.1%) with 46.4% in the PD-L1-positive subgroup (>25% expression) and 0% in the PD-L1-negative subgroup (<25% expression). The disease control rate at 12 months for the same subgroups was 57.1% and 28.6%, respectively. Responders in the PD-L1-positive subgroup had a median time to response of 6.3 weeks (95% CI, 5.6–12.1 weeks). Overall, this study demonstrated an effective and durable response rate with an acceptable safety profile.

In an update of the expansion cohort from the same trial (NCT01693562), 191 patients were enrolled with a significant proportion with relatively poor prognosis, 97% of whom had previous platinum-based therapy. In addition, 95% had visceral metastases and 49% had liver metastases.24 In the cohort, the ORR was 17.8% (95% CI, 12.7%–24.0%), which included seven patients with a complete response. The ORRs in PD-L1-positive patients was 27.6% (95% CI, 19.0%–37.5%) compared with 5.1% (95% CI, 1.4%–12.5%) in PD-L1-negative patients. The response rate in other subgroups was also significant. In patients with lymph node metastases, the ORR was 50.0% (95% CI, 23.0%–77.0%). In patients with visceral metastases or liver metastases, the ORR was 15.3% (95% CI, 10.3%–21.4%) and 7.3% (95% CI, 2.7%–15.2%), respectively. With limited follow-up, the progression-free survival (PFS) was 2.1 months (95% CI, 1.4–2.8) in the PD-L1-positive group and 1.4 months in the PD-L1-negative group (95% CI, 1.3–1.5). In addition, the data for OS were immature, but the authors report a median OS of 18.2 months in the treated group. The safety profile report consisted of common AEs, which were fatigue.

### Table 1 Approved drugs for locally advanced or metastatic urothelial carcinoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Trial</th>
<th>Indication</th>
<th>Phase</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>NCT02108652</td>
<td>Cis-ineligible or progression on platinum</td>
<td>II</td>
<td>15</td>
<td>7.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>NCT01772004</td>
<td>Progression on platinum</td>
<td>Ib</td>
<td>18.2</td>
<td>13.7</td>
<td>11.6 (w)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>NCT02256436</td>
<td>Progression on platinum</td>
<td>III</td>
<td>21.1</td>
<td>10.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-L1</td>
<td>NCT02387996</td>
<td>Progression on platinum</td>
<td>II</td>
<td>19.6</td>
<td>8.7</td>
<td>NR</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>NCT01693562</td>
<td>Progression on platinum</td>
<td>I/I</td>
<td>17.8</td>
<td>18.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Abbreviations:** ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; NR, non-reported; w, weeks.
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Review of durvalumab

(19.4%), decreased appetite (9.4%), diarrhea (8.4%), and rash (7.3%). Overall, grade 3 or 4 treatment-related AEs occurred in 6.8% of the trial cohort.

Currently, the Phase III trial DANUBE (NCT02516241) is evaluating durvalumab in the first-line setting in patients with locally advanced or metastatic urothelial carcinoma. In this trial, patients are randomized to durvalumab monotherapy, durvalumab combination therapy with tremelimumab (anti-CTLA-4 antibody), or standard of care chemotherapy (either cisplatin–gemcitabine or carboplatin–gemcitabine). Patients are further stratified by eligibility to receive chemotherapy based on the PD-L1 expression and the presence or absence of visceral metastases. The primary endpoints are PFS and OS. To date, the results are pending.

Despite the success of monotherapy, there are still patients who progress or do not respond to initial treatment, which sparked an interest in combination therapy. Ongoing trials include BISCAY (NCT02546661), which is a Phase Ib trial recruiting patients with metastatic UC who are randomized to durvalumab in combination with multiple agents (durvalumab monotherapy, durvalumab + AZD4547 [fibroblast growth factor receptor tyrosine kinase family inhibitor], durvalumab + olaparib [poly(ADP-ribose) polymerase inhibitor], durvalumab + AZD1775 [Weel kinase inhibitor], and durvalumab + vistusertib [mammalian target of rapamycin]) with primary safety endpoint. This trial will be offered to patients who are immunotherapy naive. In the Phase II BASKET study (NCT02527434), patients with metastatic urothelial cancer with or without prior treatment with PD1 or PD-L1 inhibitors were recruited to receive the combination of tremelimumab with durvalumab. The primary endpoint is objective response rate, and the results of this study are still pending. Finally, a combination of durvalumab and tremelimumab with or without a toll-like receptor 3 agonist (PolyICLC) is being evaluated in a Phase I/II trial (NCT02643303) with the primary endpoint being safety and tolerability as well as ORR, PFS, and OS.

Non-muscle-invasive bladder cancer (NMIBC)

Current therapies

Treatments for NMIBC represent the earliest forms of immunotherapy for bladder cancer. The introduction of BCG to the armamentarium by the urologist was revolutionary as it provided a local treatment with manageable side effects with durable efficacy and is currently the preferred adjuvant treatment for high-risk NMIBC.27 Although the exact underlying mechanisms of the efficacy of intravesical BCG are incompletely elucidated, it is generally accepted that immune response to BCG plays a part28 in conjunction with both urothelial cells and bladder cancer cells.29 However, there is a high failure rate associated with BCG treatment that includes recurrence and more worrisome, progression. Furthermore, production shortages for BCG have placed constraints on treatment of NMIBC. As such, there is an increased pressure for other treatment strategies with similar efficacy. Current treatments center upon chemotherapeutic agents delivered intravesically in the second-line setting such as mitomycin C, thiopeta, gemcitabine, docetaxel, valrubicin, and epirubicin with different combinations thereof with or without immune modulators (eg, interleukin-15).

There has been great interest in potentiating the immune system as it has clearly worked using BCG. The excitement with the efficacy of checkpoint inhibitors in the advanced UC setting has spilled over to the NMIBC setting. This is reasonable as PD-L1 expression in tumor cells has been associated with prior BCG treatment, perhaps pointing to a potential resistance mechanism.30 Currently, there are a number of trials incorporating checkpoint inhibitors in the second-line setting. For example, an ongoing Phase II trial (NCT02844816) is evaluating the complete response rate in BCG-unresponsive patients using IV atezolizumab every 21 days for up to 17 courses (51 weeks) in the absence of disease progression or unacceptable toxicity. Another Phase II trial (NCT02625961) is evaluating pembrolizumab (IV 200 mg Q3 weeks) in BCG-unresponsive patients. Treatment duration is 24 months or until disease recurrence or progression, unacceptable toxicity, withdrawal, or investigator decision. The patients are further stratified by the presence or absence of CIS based on tissue pathology at screening. Follow-up plan is cystoscopy and urine cytology every 12 weeks for the first 2 years, every 24 weeks for the following 2 years, and every 52 weeks thereafter. Co-primary endpoints are complete response rate and disease-free survival. Other strategies are to combine checkpoint inhibitors with BCG. A Phase Ib/II trial (NCT02792192) is assessing the safety and tolerability of IV atezolizumab infusion alone and in combination with intravesical BCG in high-risk NMIBC patients. Other strategies include using intravesical checkpoint inhibitors, as a current Phase I dose escalation trial (NCT02808143) aims to assess the safety of combination intravesical BCG and pembrolizumab in patients with refractory NMIBC.

Durvalumab in NMIBC

Given the evidence that durvalumab is effective in advanced setting, currently, it is being studied in patients with non-muscle-invasive disease. A Phase II trial (NCT02901548)
is under way to assess the combination of IV durvalumab and BCG in patients with BCG-refractory disease. The main inclusion criteria are high-grade carcinoma in situ (CIS) at 6 months after BCG treatment, progression at 3 months after induction BCG, recurrence of high-grade CIS, or persistent CIS noted in the bladder biopsies within 3 months of completing at least two induction treatments with BCG. Patients will be assigned to a single arm of IV durvalumab 1,500 mg/kg Q4 weeks for a total of 12 months. Posttreatment assessment will include cystoscopy with biopsy and transurethral resection of the bladder tumor (TURBT) at baseline, 3, 6, 9, 12, 18, and 24 months after the first treatment. Mapping biopsies will be conducted at 6 and 24 months. The primary outcome is complete response rate at 6 months, whereas the secondary endpoint is complete response rate at 24 months.

**Conclusion**

In the past decade, the use of monoclonal antibodies to unshackle T-cells from their checkpoint inhibition has revolutionized immunotherapy, but the treatment remains fettered by unreliable responses, late relapses, unpredictable autoimmune phenomena, and complex microenvironment interactions limiting our ability to select likely responders. Both innate and adaptive checkpoint inhibitor resistances have been described, and the field is rapidly accumulating whole-exome sequencing data correlated with clinical information to tease apart the nuances of the complicated interaction between the immune system and the cancer growth. Human leukocyte antigen heterogeneity, mutational load, TCR clonality, and T-cell tumor penetration are all active areas of interest.

While we are awaiting the results of further translational research, clinical data continue to amass. Investigators of checkpoint inhibitor clinical trials have strategized to manipulate subpar ORR by bringing the agents front line or as neoadjuvant treatment, more carefully selecting patients through biomarkers and combining immunotherapies or combining approaches. These strategies have been met with variable success. More recently, attention has been directed toward combining checkpoint inhibitors with other treatments with nonoverlapping toxicities, such as chemotherapy or other inhibitors of tumor-mediated immune suppression outside the immune checkpoint pathways. While somewhat controversial, this approach stands on the foundation of work by Galluzzi et al who revealed that certain types of chemotherapy and radiation may heighten antigenicity and adjuvanticity and improve response to checkpoint inhibition.

As our treatment armamentarium for urothelial carcinoma continues to expand, checkpoint inhibitors appear at the center of the current treatment paradigm. Many trials are currently ongoing to refine our treatment strategies while exploring more novel ways to approach treatment in hopes of providing hope for an otherwise lethal disease.

**Disclosure**

The authors report no conflicts of interest in this work.

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