Chapter 18
Safety of Immune Checkpoint Inhibitors in the Peri-operative Setting

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Principles of Immune Checkpoint Blockade

In recent years, immune checkpoint inhibitors (ICIs) have become a mainstay of modern cancer immunotherapeutics. ICIs are capable of increasing the amplitude of the systemic antitumor immune response through the inhibition of immune checkpoint proteins such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4; alternatively called CD152), programmed cell death protein 1 (PD1; alternatively called CD279), and programmed death-ligand 1 (PDL1; alternatively called CD274 or B7-H1) [1]. In normal cells, these proteins function as inhibitory molecules that maintain immune tolerance through modulation of the immune system. Specifically, CTLA4 dampens T-cell activation, while PD1 and PDL1 function in concert to reduce both T-cell activation and T-cell effector function in activated T-cells [2]. Interestingly, cancer cells often avoid T-cell-mediated destruction in the tumor microenvironment (TME) by presenting PDL1 on the cell surface as part of both innate and adaptive immune resistance mechanisms [3–5]. Thus, the goal of immune checkpoint blockade (ICB) is to revive antitumor immunity mainly via anti-CTLA4, anti-PD1, and anti-PDL1 therapies. In clinical practice, ICIs have demonstrated high efficacy in a subset of patients, and several ICIs are approved for use in the treatment of various malignancies at varying stages, including genitourinary cancers [6].

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A. Necchi, P. E. Spiess (eds.), *Neoadjuvant Immunotherapy Treatment of Localized Genitourinary Cancers*,
https://doi.org/10.1007/978-3-030-80546-3_18

Approved Indications for ICIs in Genitourinary Malignancies

In the treatment of urothelial carcinomas of the bladder (UC), atezolizumab (anti-PDL1) and pembrolizumab (anti-PD1) are approved for use by the United States Food and Drug Administration (FDA) as first-line agents in patients with advanced or metastatic disease who are not candidates for platinum-based chemotherapy [7]. In the second-line setting, nivolumab (anti-PD1) and durvalumab (anti-PDL1) are approved for use when patients have locally advanced or metastatic disease and have failed platinum-based chemotherapy [8, 9]. In patients with locally advanced or metastatic disease who have not progressed on platinum-based chemotherapy, avelumab (anti-PDL1) can be used as maintenance therapy [10]. Currently, pembrolizumab is the only approved drug for organ-confined disease, specifically, as a second-line option in patients who are Bacillus Calmette-Guerin (BCG)-unresponsive, are ineligible for cystectomy, and do not show evidence of muscle invasion. Thus, immune checkpoint blockade therapy is not approved for use in the peri-operative setting for patients with muscle-invasive or locally advanced disease (i.e., cT2-T4NXM0). Of note, no anti-CTLA4 therapies are approved to treat urothelial carcinoma, but pre-clinical and clinical investigations are ongoing [11].

In the treatment of renal cell carcinoma (RCC), nivolumab and ipilimumab (anti-CTLA4) are approved in combination for use in treatment-naïve patients with poor- to intermediate-risk advanced RCC [12]. Avelumab is approved for use in combination with axitinib – a small molecule tyrosine kinase inhibitor (TKI) – in the first-line setting for untreated, advanced RCC [13]. Pembrolizumab is also approved in combination with axitinib, but in patients with advanced RCC who have no prior exposure to systemic treatment [14]. While there are multiple immunotherapy options available to patients with advanced disease, there are no ICIs approved for use in patients with localized disease, including those who are ineligible for surgical resection of the tumor (partial or radical nephrectomy).

Finally, within the setting of prostate cancer, there is a paucity of ICIs approved for use. Specifically, pembrolizumab is approved for use only in the treatment of castration-resistant prostate cancer (CRPC) in patients who have exhausted all available treatment options (i.e., androgen deprivation therapy, chemotherapy, second-generation hormone therapy, radium-223, sipuleucel-T) and have progressed. These patients must also exhibit microsatellite instability in the tumor and/or possess mutations in DNA mismatch repair (MMR) genes [15].

ICI Immune-Related Toxicities

As described, immune checkpoint inhibitors are currently seldom used to treat patients with localized genitourinary malignancies in the peri-operative setting outside of a clinical trial. This is in part due to the potential albeit rare likelihood of the development of immune-related adverse events (irAEs) that could delay surgery or

lead to worse surgical outcomes. In a 2019 meta-analysis of treatment-related adverse events (AEs) in 20,128 patients across 125 clinical trials investigating anti-PD1 and anti-PDL1 therapies, including 22 trials on genitourinary cancers, nearly 2 in 3 patients experienced ≥1 AE, and 1 in 7 patients experienced ≥1 grade 3 or higher AE. Fatigue (18.3%; 95% CI: 16.5–20.1), pruritus (10.6%; 95% CI: 9.5–11.8), and diarrhea (9.5%; 95% CI: 8.4–10.6) were the most common all-grade AEs, while fatigue (0.9%; 95% CI: 0.7–1.1), anemia (0.8%; 95% CI: 0.6–1.02), and aspartate aminotransferase (AST) increase (0.8%; 95% CI: 0.6–0.9) were the most common grade 3 or higher AEs. Immune-related adverse events were divided into endocrine dysfunctions and all other irAEs (Table 18.1). Hypothyroidism (6.1%; 95% CI: 5.4–6.9) and hyperthyroidism (2.8%; 95% CI: 2.4–3.3) were the most common all-grade irAEs, while hyperglycemia (0.24%; 95% CI: 0.1–0.4), adrenal insufficiency (0.18%; 95% CI: 0.1–0.3), type 1 diabetes (0.18%; 95% CI: 0.1–0.3), hypophysitis (0.16%; 95% CI: 0.1–0.3), and hypothyroidism (0.08%; 95% CI: 0.04–0.1) were the most common grade 3 or higher irAEs. Among all other irAEs, diarrhea (9.5%; 95% CI: 8.4–10.6), AST increase (3.4%; 95% CI: 2.9–3.9), vitiligo (3.3%; 95% CI: 2.8–3.8), alanine aminotransferase (ALT) increase (3.1%; 95% CI; 2.7–3.6), pneumonitis (2.8%; 95% CI: 2.4–3.2), and colitis (1.2%; 95% CI: 0.9–1.5) were the most common all-grade irAEs. AST increase (0.75%; 95% CI: 0.6–0.9), ALT increase (0.70%; 95% CI: 0.5–0.9), pneumonitis (0.67%; 95% CI: 0.5–0.9), diarrhea (0.59%; 95% CI: 0.5–0.8), and colitis (0.47%; 95% CI: 0.3–0.7) were the most common grade 3 or higher irAEs. The overall mean incidence of AEs was 1.7% (95% CI: 1.4–2.0) in the genitourinary cancer studies examined, and this did not vary significantly compared to other cancer types evaluated in the meta-analysis. Overall, 82 treatment-related deaths were observed with respiratory causes resulting in 48% of treatment-related deaths (pneumonitis was the most common; 28%) [16]. As noted in the study, some of the lower-grade irAEs can be early indicators of more serious irAEs; thus, timely management of irAEs using available guidelines is necessary [17–19]. In general, initial management of many irAEs (e.g., dermatologic/mucosal, diarrhea/colitis, hepatotoxic, pneumonitis) may involve treatment with immunosuppressive medications, such as glucocorticoids and either

Table 18.1 Most common endocrine irAEs and non-endocrine irAEs in clinical trials investigating anti-PD1 and anti-PDL1 therapies

Endocrine irAEs	Non-endocrine irAEs
All-grade: Hypothyroidism (6.1%) Hyperthyroidism (2.8%) Hyperglycemia (1.2%)	All-grade: Diarrhea (9.5%) AST increase (3.4%) Vitiligo (3.3%) Alanine aminotransferase (ALT) increase (3.1%)
Grade ≥ 3: Hyperglycemia (0.24%) Adrenal insufficiency (0.18%) Type 1 diabetes (0.18%) Hypophysitis (0.16%) Hypothyroidism (0.08%)	Grade ≥ 3: AST increase (0.75%) ALT increase (0.70%) Pneumonitis (0.67%) Diarrhea (0.59%) Colitis (0.47%)

temporary or permanent discontinuation of the ICI. For more severe irAEs that do not improve with glucocorticoid use, other immunosuppressives such as infliximab may be provided [17–19].

Based on the current literature, patients who are treated with anti-CTLA4 therapy (e.g., ipilimumab) experience irAEs more frequently than those who are treated with anti-PD1/anti-PDL1 therapy (e.g., nivolumab). For example, 71% of patients experienced irAEs in a pooled analysis of four clinical trials involving nivolumab, while 85% of patients experienced irAEs while receiving ipilimumab. Interestingly, the use of immunosuppressive medications in the management of irAEs did not adversely impact objective response to immunotherapy in the nivolumab trial or overall survival (OS) in the ipilimumab trial [20, 21]. Other studies report similar findings regarding the greater incidence of irAEs in anti-CTLA4-treated patients versus anti-PD1/PDL1-treated patients across multiple classes of irAEs, including systemic irAEs (e.g., fatigue), dermatologic/mucosal irAEs, diarrhea/colitis, and pneumonitis [22–27].

Potential Benefits of ICI Use in the Peri-operative Setting

Given that utilization of ICIs is rare peri-operatively, it is difficult to accurately evaluate the potential risks of neoadjuvant and adjuvant ICI use due to the paucity of clinical data available. With respect to the potential benefits of neoadjuvant immunotherapy, pre-clinical and limited clinical studies have shown that ICI use prior to surgery may lead to a reduction in tumor burden (rendering potentially highly challenging or non-resectable tumors into those highly amenable to extirpation), eliminate/control micrometastatic disease, and help improve recurrence-free survival (RFS) and overall survival (OS) – all of which are potential benefits of a conventional neoadjuvant systemic chemotherapeutic approach as well [28–30]. However, neoadjuvant immunotherapy may offer additional benefits most notably in those with imperative contraindication to effective chemotherapy such as pre-treatment renal impairment, neurotoxicity, or hearing loss, e.g.

First, patients with contraindications to chemotherapy can be offered neoadjuvant ICIs as an alternative with fewer side effects. In fact, a recent meta-analysis of 22 clinical trials involving 12,727 patients compared the incidence of AEs in patients treated with ICIs (anti-CTLA4, anti-PDL1, and anti-PD1) versus standard-of-care (SOC) chemotherapy; the authors found that only 16.5% of patients treated with immunotherapy experienced a grade 3 or higher AE, versus 41.1% of patients who were treated with SOC chemotherapy. The patients treated with immunotherapy were also overall less likely to experience an AE, discontinue treatment, or experience death secondary to a treatment-related AE [31]. However, the subset of immune-related adverse events that occur uniquely as a result of immune checkpoint blockade must be noted [32]. Second, given that the primary tumor is the principal source of tumor antigen, neoadjuvant ICI use would result in enhanced activation and expansion of tumor-specific T-cells compared to the immune response

observed in immunotherapy delivered in the absence of primary tumor. This phenomenon has been demonstrated in both pre-clinical and clinical models of solid, resectable tumors [29, 33].

In the adjuvant setting, immune checkpoint blockade in the immediate post-operative period could be used to mitigate the negative effects of the surgical stress response, specifically, changes in angiogenic, inflammatory, endocrine, and immunosuppressive signaling pathways that can improve the survival of any residual cancer cells and potentially contribute to disease recurrence [34–37].

Currently, there are a number of recent trials investigating peri-operative use of immune checkpoint blockade for genitourinary malignancies. While a portion of the efficacy data has not been published, early safety data on both irAEs and surgery-related complications have been released. Thus, the purpose of this chapter is to provide a summary of the latest bladder, kidney, and prostate cancer clinical trials investigating peri-operative immunotherapy and review available pre- and peri-operative safety data from these clinical investigations.

Peri-operative Immunotherapy in Bladder Cancer

In the setting of urothelial carcinoma of the bladder, the American Urological Association (AUA) recommends definitive therapy (i.e., radical cystectomy; RC) for patients who have muscle-invasive disease (MIBC), do not have involvement beyond the common iliac lymph nodes, and have no evidence of distant metastases. Prior to surgery, neoadjuvant cisplatin-based chemotherapy (NAC) is recommended for eligible patients. If patients do not receive cisplatin-based NAC and demonstrate non-organ-confined disease at cystectomy (pT3/T4a and/or N+), they are recommended to receive adjuvant cisplatin-based NAC [38].

While cisplatin-based NAC is widely recommended for MIBC and has demonstrated an overall survival benefit, utilization remains relatively low [39–41]. Nearly half of patients are ineligible due to contraindications such as renal insufficiency, and those who are prescribed cisplatin-based NAC experience major toxicities [42, 43]. Given that recurrence rates are high after surgery alone, aggressive treatment upfront is critical in the management of MIBC [44]. Thus, peri-operative immune checkpoint blockade may expand the number of patients eligible for systemic neoadjuvant or adjuvant treatment and lead to improved MIBC outcomes. Given that the tolerability of neoadjuvant systemic therapy is of paramount importance, the purpose of this section is to review safety data from ongoing clinical investigations. Currently, there are five completed or ongoing clinical trials evaluating the use of neoadjuvant ICIs for MIBC that have safety data available. In the adjuvant setting, there is a paucity of data from prospective clinical trials evaluating either chemotherapy or ICIs; specifically, only one trial will be discussed. Finally, a single trial investing peri-operative immune checkpoint blockade therapy (i.e., neoadjuvant and adjuvant) will be reviewed. Table 18.2 summarizes the safety findings from these trials.

Table 18.2 Most commonly reported medical irAEs and surgical complications in MIBC ICI trials

Trial (NCT #)	Agent(s)	Most common toxicities
PURE-01 (NCT02736266)	Pembrolizumab (anti-PD1)	Medical: Thyroid dysfunction (all-grade), AST/ALT increase, pruritus, pyrexia Surgical: Sepsis, subocclusion
ABACUS (NCT02662309)	Atezolizumab (anti-PDL1)	Medical: Fatigue, anorexia, transaminitis, pruritus Surgical: UTI, paralytic ileus, anemia, wound dehiscence
NABUCCO (NCT03387761)	Ipilimumab (anti-CTLA4) and nivolumab (anti-PD1)	Medical: Increased lipase, ALT increase, diarrhea Surgery: NA
NCT02812420	Durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4)	Medical: Hepatitis, amylase/lipase increase Surgery: NA
DUTRENEO (NCT03472274)	Durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4)	Medical: 21.7% of patients experienced grade 3 or 4 irAEs Surgical: NA
IMvigor010 (NCT02450331)	Atezolizumab (anti-PDL1)	Medical: 16% of patients experienced grade 3 or 4 irAEs Surgical: NA
SAKK 06/17 (NCT03406650)	Durvalumab (anti-PDL1)	Medical: 24% of patients experienced grade 3 or 4 irAEs Surgical: Infection

Abbreviations: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *UTI* urinary tract infection, *NA* not available

Single-Agent Neoadjuvant Immunotherapy Clinical Trials in MIBC

The PURE-01 trial is a phase 2, open-label, single-arm study of pembrolizumab (anti-PD1) (3 cycles, 200 mg every 3 weeks) as a neoadjuvant therapy for cT2-3bN0M0 predominant urothelial carcinoma histology MIBC [45]. In total, 50 patients were treated with pembrolizumab followed by radical cystectomy, with a median time to RC of 22 days (IQR 15–30). With respect to medical AEs, there were 28 grade 1–2 AEs and 3 grade 3 or higher AEs observed, with thyroid dysfunction representing the most common all-grade medical AE (18%). One patient experienced an increase in AST/ALT and discontinued pembrolizumab. Additionally, the grade 1–2 AEs of pruritus (6%), pyrexia (6%), and xerostomia (4%) all had a post-RC onset within 2 months of surgery. Notably, neoadjuvant pembrolizumab did not result in any delays in surgery. With respect to surgical AEs, 30% of patients experienced a >2 Clavien-Dindo complication, with sepsis (20%) and subocclusion (16%) being the most common. The authors reported that the post-surgery complications observed were in line with previous literature on robotic-assisted and open radical cystectomies [46].

The ABACUS trial is a phase 2, open-label, single-arm study of atezolizumab (anti-PDL1) (1–2 cycles, 1200 mg every week) as a neoadjuvant therapy for cT2-T4aN0M0 MIBC in patients who either refused or were ineligible for cisplatin-based NAC and have no evidence of nodal or metastatic disease [47]. In total, 95 patients were treated with atezolizumab ($n = 75$ received 2 cycles; $n = 20$ received 1 cycle), and 87 patients underwent radical cystectomy, with a median time to RC of 39 days (IQR 28–48). Of the eight patients who did not proceed with RC, three could not receive a RC due to atezolizumab-related AEs; specifically, these irAEs were pneumonia, myocardial infarction, and deterioration of performance status. With respect to medical AEs, 52% of patients experienced at least one all-grade irAE, 11% of patients experienced a grade 3 or 4 AE, and one patient died due to dyspnea. In total, there were $n = 99$ grade 1–2 irAEs, $n = 14$ grade 3–4 irAEs, and $n = 1$ grade 5 irAE. In general, fatigue (21%), anorexia (8%), transaminitis (7%), and pruritus (7%) were the most common irAEs. In regard to surgical AEs, 45% of patients who underwent RC experienced grade 1–2 Clavien-Dindo surgical complications. The most common grade 1–2 complications were urinary tract infection (UTI) (26%), paralytic ileus (7%), and anemia (6%). Only 17% of patients experienced a grade 3–4 Clavien-Dindo surgical complication, of which the most common was wound dehiscence. Finally, one patient died post-operatively due to cardiovascular complications.

Combination Neoadjuvant Immunotherapy Clinical Trials in MIBC

The remaining clinical trials investigating neoadjuvant immunotherapy reported here used a combination therapy approach.

The NABUCCO trial is a single-arm, open-label, feasibility study of ipilimumab (anti-CTLA4) and nivolumab (anti-PD1) (2 doses each, 3 mg kg^{-1}) as neoadjuvant combination therapy for cT3-4aN0N0 and cT1-4aN1-3 M0 urothelial carcinoma in patients who either refused or were ineligible for cisplatin-based NAC. Of note, the NABUCCO trial included patients with lymph node metastases (42%) and one patient with upper tract urothelial carcinoma (UTUC) (unlike the PURE-01 and ABACUS trials) [48]. Additionally, the primary endpoint of the NABUCCO trial was the feasibility to perform surgery within 12 weeks of beginning immune checkpoint blockade therapy. In total, 24 patients were treated with neoadjuvant ipilimumab and nivolumab, followed by radical cystectomy or nephro−/urethrectomy. 75% of patients were able to tolerate the three treatment cycles, while the remaining 25% did not receive the second nivolumab dose due to irAEs. Overall, 100 of patients experienced at least one all-grade irAE, while 41% of patients experienced grade 3–4 irAEs with increased lipase (25%), ALT increase (12%), and diarrhea (12%) being the most common. Additionally, the primary endpoint of resection within 12 weeks was achieved for 23/24 (96%) of patients, while 1 patient

experienced delayed resection due to an irAE of hemolysis. Interestingly, the authors did not share data on surgical AEs or post-operative complications.

The following two neoadjuvant immunotherapy trials that will be discussed here are both investigating the use of durvalumab (anti-PDL1) in combination with tremelimumab (anti-CTLA4). Both studies have not yet published their final results, but limited safety data is available. First, NCT02812420 is a single-arm, open-label pilot study in patients with cT2-T4a MIBC who were either ineligible for or refused cisplatin-based NAC [11]. Patients are scheduled to receive two doses of combined durvalumab and tremelimumab at weeks 1 and 5, followed by radical cystectomy between weeks 9 and 11. Per available data, the study has enrolled 28/35 patients, and 21/35 have undergone both neoadjuvant ICI therapy and surgery. The authors reported grade 3 or 4 irAEs in 17% (5/28) patients, noting hepatitis and amylase/lipase increases without indicating the frequency of these irAEs. Additionally, only 2/28 (7%) of patients were required to delay surgery for >4 weeks due to irAEs. The authors of NCT02812420 did not share data on surgical AEs or post-operative complications.

The second trial, called the DUTRENEO trial, is a phase 2, open-label, multi-arm study in patients with cT2-T4aN≤1 MIBC [49]. Unlike the other trials discussed, the DUTRENEO trial enrolled patients who were eligible for cisplatin-based NAC. Following enrollment, patients were further stratified by a pro-inflammatory interferon-gamma signature (tumor immune score, TIS). Patients who exhibited a "hot" tumor were randomized to receive either combined durvalumab (1500 mg) and tremelimumab (75 mg) (3 cycles, every 4 weeks) or standard-of-care cisplatin-based NAC, while patients who exhibited a "cold" tumor received SOC cisplatin-based NAC and were not randomized. In total, 16 patients were in the cisplatin-based NAC "cold" arm, 22 patients were in the cisplatin-based NAC "hot" arm, and 23 patients were in the "hot" ICI arm. With respect to medical AEs, 62.5% and 36.4% of patients experienced grade 3 or 4 AEs in the "cold" and "hot" cisplatin-based NAC arms, while only 21.7% of patients experienced grade 3 or 4 AEs in the "hot" ICI arm. The majority of patients in all three groups completed cystectomy; specifically, 93.8%, 90.9%, and 87.0% of patients completed surgery in the cisplatin-based NAC "cold" arm, cisplatin-based NAC "hot" arm, and ICI arm, respectively. The full results of the investigation are not yet published; thus, the authors did not share data on surgical AEs or post-operative complications.

Adjuvant Immunotherapy Clinical Trials in MIBC

Currently, there are limited data available on investigations of adjuvant immune checkpoint blockade. The IMvigor010 trial is a phase 3, open-label, randomized trial of adjuvant atezolizumab versus observation in patients with either (1) pT2-4a or pN+ if patients had cisplatin-based NAC or (2) pT3-4a or pN+ if they did not receive cisplatin-based NAC due to ineligibility or refusal [50]. Patients were eligible if they underwent a radical cystectomy/nephroureterectomy within 14 weeks

of study enrollment. Patients were randomized to either receive atezolizumab (16 cycles, 1200 mg every 3 weeks) or continue on observation following surgery. With respect to medical AEs, grade 3 or 4 irAEs were observed in 16% of patients treated with atezolizumab. While the authors do not indicate the number, patients who discontinued ICI treatment commonly did so due to skin and gastrointestinal irAEs.

Combination of Adjuvant-Neoadjuvant Immunotherapy Clinical Trials in MIBC

As mentioned, early results from a single trial evaluating combined neoadjuvant and adjuvant ICI therapy are available.

The SAKK 06/17 trial is a phase 2, open-label, single-arm trial of durvalumab in combination with cisplatin or gemcitabine in patients with cT2-T4a MIBC or UTUC [51]. Unlike previous trials discussed, this study evaluated immunotherapy in combination with chemotherapy. In total, 33 patients with MIBC and 1 patient with UTUC were enrolled, and all 34 patients received the combination therapy. Cisplatin/gemcitabine was administered over four cycles every 3 weeks, while durvalumab (1500 mg) was administered in combination with cisplatin/gemcitabine for three cycles pre-operatively and continued as a single agent for a total of ten cycles post-operatively. With respect to medical AEs, 24% of patients experienced grade 3 or 4 irAEs. Notably, surgery was performed without delays in 30 of 34 patients. Of the four patients who did not undergo surgery, three patients declined surgery, and one patient was ineligible for surgery due to a "frozen pelvis" upon assessment. Overall, 27% of patients experienced Clavien-Dindo complications that were grade 3 or higher; specifically, infections represented the most frequent complication (17%).

Peri-operative Immunotherapy Clinical Trials in Kidney Cancer

In the setting of a suspected, localized case of renal cell carcinoma (RCC), the AUA recommends definitive therapy in the form of a partial nephrectomy or radical nephrectomy, with a nephron-sparing approach preferred for clinically localized renal masses due to similar oncologic outcomes of both approaches for low-stage (T1-T2N0M0) disease [52, 53]. However, a subset of patients with an intermediate-high risk of recurrence have a paucity of systemic treatment options in the peri-operative setting, as previous trials using targeted agents have not demonstrated a survival benefit [54, 55]. However, a number of recent trials have emerged investigating immune checkpoint inhibitors in the adjuvant setting after resection of

localized disease; in this section, three ongoing trials will be mentioned. Of note, none of these trials have published any data.

The KEYNOTE-564 trial is a phase 3, randomized, double-blind, placebo-controlled study of adjuvant pembrolizumab for patients with intermediate- to high-risk RCC (pT2N0M0, grade 4 or sarcomatoid; pT3N0M0, any grade; pT4N0M0, any grade; pTanyN+M0, any grade; M1 NED). The patients will receive either placebo or pembrolizumab (17 cycles, 200 mg every 3 weeks). Treatment will be stopped due to drug-related toxicities or disease recurrence. The primary and secondary endpoints are disease-free survival (DFS) and OS, respectively [56]. As noted, results are forthcoming.

The IMmotion010 trial is a phase 3, randomized, double-blind, placebo-controlled study of adjuvant atezolizumab for patients with high-risk RCC (T2, grade 4; T3a, grades 3–4; T3b/c, any grade; T4, any grade; TxN+, any grade). The patients will receive either placebo or atezolizumab (16 cycles/1 year, 1200 mg every 3 weeks). The primary and secondary endpoints include DFS and OS, respectively [57]. As noted, results are forthcoming.

The RAMPART trial is a phase 3, randomized study of adjuvant durvalumab alone (every 4 weeks for 1 year), durvalumab (every 4 weeks for 1 year) in combination with tremelimumab (2 doses), or active surveillance for patients with intermediate-high risk of recurrence, based on the Leibovich score [3–11]. The primary endpoints are DFS and OS [58]. As noted, results are forthcoming.

Peri-operative Immunotherapy Clinical Trials in Prostate Cancer

Due to early detection of disease and the relatively low risk of prostate cancer-specific mortality for the majority of patients treated with definitive therapy, there is limited interest in neoadjuvant or adjuvant systemic therapies for patients with very-low- to intermediate-risk, clinically localized disease [59–66]. In the setting of high- to very-high-risk disease, management includes radical prostatectomy, radiotherapy, and/or androgen deprivation therapy and leads to favorable outcomes [67]. For example, 10-year prostate cancer-specific survival has been shown to range between 83 and 93% in patients treated with radical prostatectomy [68]. Thus, a single trial evaluating neoadjuvant immunotherapy will be briefly mentioned.

NCT03753243 is a phase 2, open-label, single-arm study of neoadjuvant pembrolizumab combined with enzalutamide for patients with high-risk, localized prostate cancer (cT3a, Gleason grades 8–10, PSA > 20 ng/mL) who are scheduled to undergo radical prostatectomy. Patients will receive pembrolizumab (200 mg every 3 weeks) and enzalutamide (160 mg/day) for a period of 14–16 weeks. The primary endpoint is pathologic complete response, and the secondary endpoints include safety and biochemical complete response [69]. As noted, results are forthcoming.

Conclusion

This chapter provided a brief summary of current investigations into the peri-operative use of immune checkpoint inhibitors in the management of genitourinary malignancies. Specifically, early safety data from several trials in MIBC, RCC, and prostate cancer were summarized, including both drug-related toxicities (irAEs) and medical complications. Based on the data presented, peri-operative immunotherapy does not result in toxicities that are divergent in type or frequency from previous literature characterizing anti-PD1, anti-PDL1, and anti-CTLA4 toxicity profiles. Additionally, the trials discussed here do not report delays in surgery for the vast majority of patients who were treated with neoadjuvant immunotherapy. These data, pending final reports and further investigations, provide promising early evidence to support the feasibility and tolerability of peri-operative immunotherapy.

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