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Adaptive Immunity in Genitourinary Cancers

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Abstract

Context: While urothelial and renal cell cancers have exhibited modest responses to novel immune checkpoint inhibitors targeting the programmed death ligand 1 and its receptor, response rates in patients with prostate cancer have remained poor. The factors underlying suboptimal outcomes observed in patients treated with novel immunotherapies are still to be resolved.

Objective: To review the literature and describe the key adaptive immune physiological events associated with cancer progression and therapeutic response in genitourinary (GU) cancers.

Evidence acquisition: We performed a nonsystematic, collaborative narrative review to highlight recent advancements leading to the current state of knowledge on the critical mediators of antitumor adaptive immunity to GU cancers. Further, we discuss the findings on the pre- and post-treatment immunological events that either are unique to each of the three cancer types or exhibit overlapping clinical associations.

Evidence synthesis: Aging-associated immune function decline is a major factor underlying poor outcomes observed in patients treated with both conventional and novel immunotherapies. Other cancer immunobiological aspects associated with suboptimal responses in GU cancers include the overall tumor mutational burden, mutations in specific tumor suppressor/DNA damage repair genes (*KDM6A*, *PTEN*, *STAG2*, *TP53*, *ATM*, and *BRCA2*), and abundance of multiple functional states of adaptive immune cells and their spatiotemporal localization within the tumor immune microenvironment. Understanding these mechanisms may potentially lead to the development of prognostic and predictive biomarkers such as immune cell infiltration profiles and tertiary lymphoid structures (TLSs) that associate with variable clinical outcomes depending on

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the nature of the novel immunotherapeutic approach. Implementation of newer immune-monitoring technologies and improved preclinical modeling systems will augment our understanding of the host and tumor intrinsic factors contributing to the variability of responses to immunotherapies.

Conclusions: Despite the tremendous progress made in the understanding of dynamic and static adaptive immune elements within the tumor immune landscape, several knowledge gaps remain. A comprehensive knowledge thus gained will lead to precision immunotherapy, improved drug sequencing, and a therapeutic response.

Patient summary: We performed a collaborative review by a diverse group of experts in the field to examine our understanding of the events and crosstalk between cancer cells and the patient's immune system that are associated with responses to novel immunotherapies. An evolving understanding of tumor-intrinsic and host-related immune alterations, both before and after therapy, will aid in the discovery of promising markers of responses to immunotherapy as well as the development of unique therapeutic approaches for the management of genitourinary cancers.

1. Introduction

In 2020, cancers of the genitourinary (GU) tract originating from the kidney/renal pelvis, urinary bladder, or prostate accounted for 2.42 million newly diagnosed cancer cases worldwide. As per the International Agency for Research on Cancer, this number is estimated to increase to approximately 4.08 million new cases by 2040. A major factor underlying this projected rise in incidence is the aging global population, which remains an unmodifiable risk factor for all cancers of the GU tract. Most patients diagnosed with a cancer originating in the GU tract are >65 yr old [1]. Recent initiatives such as the Genotype-Tissue Expression Program in humans and Tabula Muris Senis in mice, which comprehensively characterized age- and sex-related transcriptomic alterations across tissue types, have advanced our understanding of the effect of biological aging on immunity within the prostate, bladder, and kidney [2,3]. Studies in the bladder and kidney have also highlighted tissue-specific local immunological changes such as increased lymphocytic infiltration, tertiary lymphoid structure (TLS) formation, or changes in the microbiome that accompany biological aging in a sex-dependent manner [4–6].

Simultaneous to the rise in incidence, newer therapies, especially those targeting the host immune system, have demonstrated considerable efficacy in cancers of the bladder and kidney [7]. Although patients with prostate cancer have not benefited as much as bladder cancer patients, those with genomic alterations such as germline or somatic mutations in DNA damage repair (DDR) genes (*BRCA2* and *ATM*) [8] have experienced indirect benefits [9].

Here, we review the key aspects of adaptive antitumor immune responses associated with carcinogenic processes within the GU tract and highlight major advances leading to the current state of knowledge on the biology and therapeutic exploitation of tumor vulnerabilities in GU cancers.

2. Evidence acquisition

We performed a comprehensive literature review using a nonsystematic approach to search original studies exploring adaptive immunity in bladder, kidney, and prostate cancer, until December 2022. From this comprehensive search using the PubMed database, we summarize the most relevant studies and outcomes from clinical trials that significantly advanced the field of immuno-oncology in GU cancers. While a majority of the original articles were published over the last 10 yr, we also include some earlier publications that were critical to the overall scope of this review. Following careful consideration of 162 publications, we selected 108 publications that were deemed most suitable by all authors to be included in this narrative review. Based on the evidence from recently completed immunotherapy trials integrating pretreatment tumor immune status in trial design, we further provide perspectives on combination approaches to improve response rates.

3. Evidence synthesis

3.1. Adaptive immunity in the healthy GU tract

The mucosal barrier in the GU tract is constantly exposed to metabolic waste products, microorganisms, and environmental carcinogens; thus, homeostatic mechanisms mediate immune tolerance at the GU interface. Tissue-resident antigen-presenting cells (APCs) such as macrophages, monocytes, and dendritic cells take up antigen, but the strength of the subsequent adaptive immune response may depend upon the type of APCs presenting antigen [10]. The macrophage is the major tissue-resident innate immune cell that acts as the first responder to infectious or carcinogenic insults at the GU mucosae [4,10–12]. To bridge adaptive immune mechanisms, other cell types, such as mast cells, dendritic cells, neutrophils, and natural killer cells located within the bladder mucosa, also play significant roles and have widely been studied in the context of antitumor immunity [13,14].

Among the cells of the adaptive immune branch, helper T cells, cytotoxic T cells, and their mucosal innate counterparts such as mucosal-associated invariant T cells, natural killer T cells, and gamma-delta ($\gamma\delta$) T cells are critical to antitumor immunity in the GU mucosa [15–19]. In one study, single-cell sequencing of tumors before and after

chemotherapy or immune checkpoint inhibition showed that, in addition to cytotoxic CD8+ T cells, bladder tumors are also enriched in clonally expanded CD4+ T cells in multiple functional states, such as regulatory or helper cells [16]. Novel findings from this study were the observation of the cytotoxic capacity of tumor-infiltrating CD4+ T cells that exhibited robust expression of the cytotoxic proteins granzyme K and granzyme B and the presence of several canonical CD4+ T-cell states such as Th17 cells. Further, bacillus Calmette-Guérin (BCG) immunotherapy-specific γδ T cells increase in the urine of patients undergoing BCG treatment [20]. A single study reported that tissue-resident memory T cells, a more recently described type of memory T cells, were positively associated with a good response to immune checkpoint inhibitors (ICIs) in muscle-invasive bladder cancer (MIBC) [21]. While diverse T-cell populations in the bladder are not well researched, it is likely that these play an important role in immunity to bladder diseases [19].

Tissue-resident B cells are rare in younger individuals. However, they significantly increase with biological aging in the kidney [22] and the bladder [23], residing mainly within mucosa-associated lymphoid tissue, commonly referred to as TLSs [4]. The formation of TLSs within the bladder and kidney also results from chronic inflammation [24] such as persistent urinary tract infection [25], prolonged exposure to carcinogens, immunotherapy [26], or age-related increased systemic levels of tumor necrosis factor-α [27]. The formation of TLSs of acute and chronic nature explains their varied associations with clinical outcomes across different cancer types [27,28]. The cellular composition, presence of activated and exhausted states, and spatial organization of TLSs under pre- and post-treatment scenarios have prompted further research into their role as predictive biomarkers for several immunomodulatory therapies, including, most importantly, ICIs [27–29].

3.2. Tumor immune landscape of GU cancers

Snapshots of dynamic immune responses and coordinated crosstalk with neighboring cells are often reflected in studies evaluating the pretreatment tumor immune microenvironment (TIME). Indeed, the pretreatment immune landscape of GU cancers has extensively been studied to identify novel therapeutic targets and immune biomarkers of response (Fig. 1). Several studies on genomic correlates of the pretreatment TIME have confirmed that the loss of tumor suppressor or DDR gene function is a key driver of coevolving TIME states in GU cancers [30].

3.2.1. Bladder cancer

Mutations in tumor suppressor or DDR genes, such as *KDM6A*, *ARID1A*, *STAG2*, *TP53*, and *PPARG*, and their association with variable TIME states have widely been reported in MIBC and non–muscle-invasive bladder cancer (NMIBC) [31,32]. In a carcinogen-induced murine model, it was shown that *KDM6A* deficiency in urothelial cells activated cytokine signaling and promoted M2 macrophage polarization in the bladder immune microenvironment [30]. Interestingly, evaluation of both normal and malignant urothelium using 2097 microbiopsies from human bladders showed mutations in *KDM6A* to be more prevalent in older women than in men [33,34]. Sequencing of bladder-associated lymphoid or immune cell aggregates (commonly found in both nonmalignant and malignant bladder tissues) revealed a low mutational allele frequency in immune cells, confirming *KDM6A* loss as a cancer cell–intrinsic event. Similarly, mutations in *STAG2* were more enriched in tumors from women than in tumors from men [35].

An investigation of the effect of the mucosal environment on bladder carcinogenesis showed a significant association between interleukin-6 (IL-6)-, IL-3–, IL-8–, IL-17–, and IL-23–regulated T- and B-cell pathways and the evolution of a basal subtype of bladder cancer [36]. A high tumor mutational burden (TMB) is often observed in these tumors and contributes to the generation of an immune-infiltrated tumor by amplifying the tumor neoantigen repertoire. By contrast, chromosomal alterations such as loss of the 9p21 region, harboring the IFN1 genes, are associated with less infiltrated TIMEs across multiple cancers, including MIBC [37]. Not surprisingly, tumors with 9p21 region loss also exhibit a poor response to immune checkpoint blockade potentially due to the loss of CDKN2A [37].

Immune-cell deconvolution analyses from tumor whole transcriptomic datasets as well as characterization of static TIME states via spatial and single-cell immune-cell profiling have defined a spectrum of pretreatment TIME states in GU cancers that correlate with disease progression and treatment outcomes [28,38,39]. Indeed, such studies have reinforced that in individuals' TIME states, adaptive immunity, and tumor-promoting inflammation may exist in a delicate balance [40]. In bulk transcriptomic data from pretreatment tumors obtained from patients with metastatic bladder cancer enrolled on a clinical trial with PD-1 blockade, the ratio of two gene signatures reflecting adaptive immunity and tumor-promoting inflammation, coined the myeloid single-cell immune:protumorigenic inflammation ratio (Msc2IR) score that correlated with the response to treatment [40]. Projecting these gene signatures onto single-cell RNA sequencing data from a cohort of patients with MIBC confirmed that the adaptive immune signature genes emanated largely from diverse cell populations, whereas the tumor-promoting inflammation signature genes emanated largely from macrophages [41].

Infiltration patterns and spatial organization of immune cells are widely shown to correlate with the basal and luminal subtypes of bladder cancer, and treatment outcomes [42]. For instance, greater CD8+ T-cell infiltration in the basal subtype of bladder cancer may confer increased susceptibility to treatment due to higher expression of immune checkpoints on exhausted phenotypes and short-term treatment benefit via immunogenic cell death–inducing chemotherapy [43].

Most recently, Aragaki et al. [44] showed that female MIBC patients with increased expression of B- and T-cell genes in their tumors had a poor response to treatment with atezolizumab immunotherapy, in contrast to male patients. Similar sex differences in increased expression of immune cell–associated transcripts and programmed death ligand 1 (PD-L1) were also reported by Hurst et al. [31], with higher expression of PD-L1 in stage T1 tumors from women,

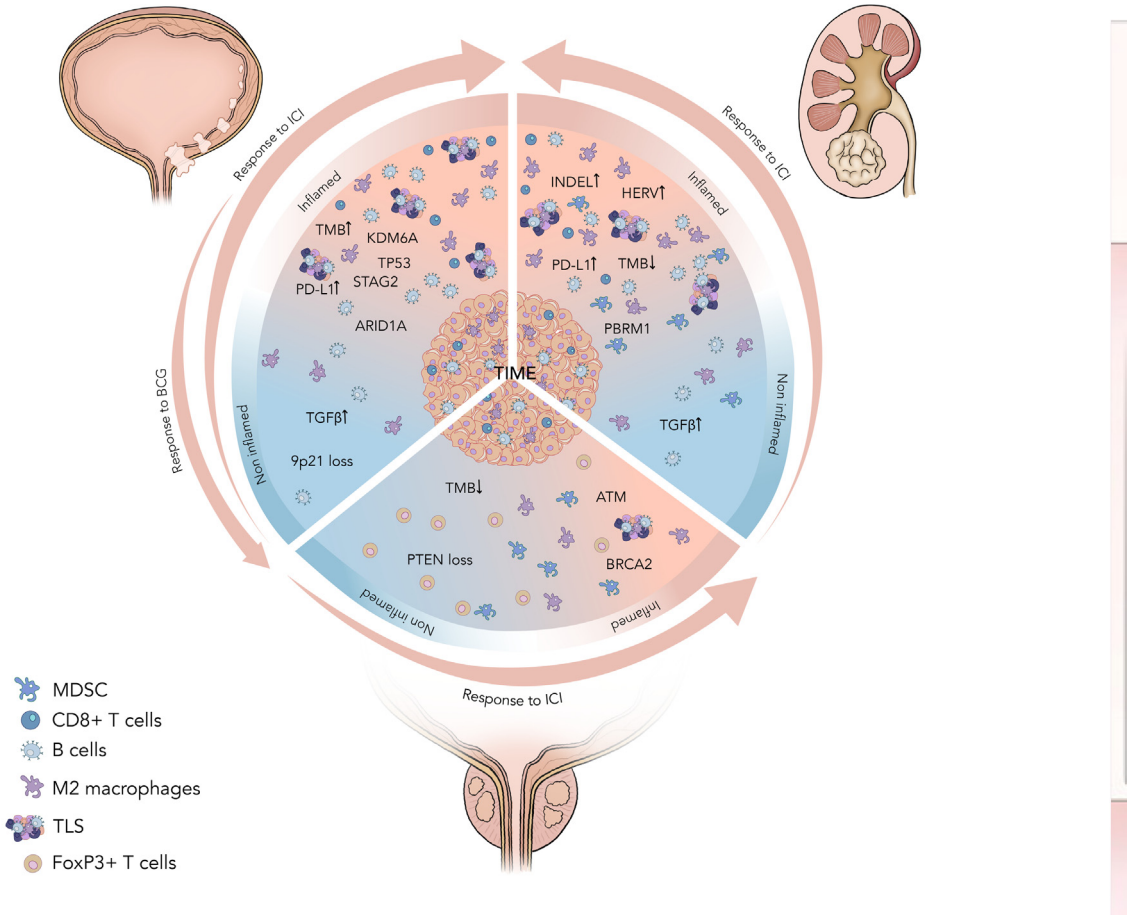

Fig. 1 – The tumor immune microenvironment of GU cancers and response to immunotherapy. The TIME of GU cancers is influenced by factors such as TMB and mutations in DDR genes (such as *TP53*, *KDM6A*, *STAG2*, *ARID1A* [bladder cancer]; *PTEN*, *ATM*, *BRCA1* [prostate cancer]; and *PRMB1* [RCC]) or due to TMB, insertion or deletion (INDEL) mutations, or human endogenous retroviral (HERV) elements. The pretreatment TIME states are observed as a spectrum ranging from noninflamed (less infiltrated) to inflamed (highly infiltrated). Inflamed TIME exhibits increased density of CD8+ T cells (and their proliferating and dysfunctional subsets), TLSs, B cells and M2-like suppressive macrophages, and PD-L1–expressing cells. Patients with inflamed pretreatment TIME generally show favorable responses to ICIs in contrast to those with noninflamed TIME. Bladder cancer patients with inflamed pretreatment TIME exhibit a poor response to BCG immunotherapy. BCG = bacillus Calmette-Guérin; DDR = DNA damage repair; GU = genitourinary; RCC = renal cell carcinoma; TIME = tumor immune microenvironment; TLS = tertiary lymphoid structure; TMB = tumor mutational burden.

although no significant associations with clinical outcomes were found. In this cohort, T1 tumors exhibited features similar to those observed in MIBC, such as increased prevalence of mutations in *ERCC2*. Further categorization of T1 tumors into T1E1, T1E2, T1E3, and T1E4 subtypes showed higher expression of genes associated with an immune response, specifically the interferon (IFN) pathway and T-cell responses. Progression after BCG was found to be higher in the subtypes T1E3 and T1E4.

Another study conducted by Taber et al. [45] on a cohort of 785 patients also showed an association between increased immune cell infiltration and higher disease stage. Interestingly, an independent association between PD-1 and PD-L1 expression with increased risks of recurrence and progression of NMIBC, in contrast to those in MIBC, was observed. Among the other immune checkpoint proteins, expression of LAG3 on stromal cells was shown to positively correlate with the abundance of exhausted CD8+ T cells [46]. This study also demonstrated increased expression of LAG3 in the basal subtype of MIBC tumors compared with the luminal subtype. While most studies to date have reported consistent findings across the known subtypes, a recent single-nucleus RNA sequencing–based profile of 48 tumors showed the presence of significant intratumoral subtype heterogeneity and the simultaneous existence of both luminal and basal characteristics within the same tumor [47]. While upper tract urothelial carcinomas constitute only 5–10% of all urothelial carcinomas, these exhibit features similar to the luminal papillary MIBC tumors, such as lower expression of genes associated with T-cell function [48]. An exploratory biomarker analysis from the ABACUS trial evaluating neoadjuvant immunotherapy in cisplatin-ineligible MIBC showed that increased baseline stromal CD8+ T cells were associated with shorter recurrence-free survival [49]. Forkhead box P3 (FoxP3+) regulatory T cells correlated positively with baseline stromal CD8+ T cells.

3.2.2. *Kidney cancer*

Clear cell renal cell carcinoma (ccRCC) is characterized by a relatively low TMB, which is about ten-fold lower than that in melanoma [50], and yet is recognized as a highly immunogenic tumor type that is responsive to

immunotherapy agents, including IL-2 [51] and ICIs [52]. The most common mutations in ccRCC include *VHL* (57–80%), *PBRM1* (35.4%), *BAP1*, *SETD2* (41.7%), *TP53* (18.8%), and *KDM5C* (16.7%) [53,54]. Among these mutations, *SETD2* mutations are associated with decreased levels of FoxP3+ T cells in the tumor core, stroma, and tumor-stroma interface; *PBRM1* mutations are associated with decreased FoxP3+ T cells in the tumor core; and *KDM5C* mutations are associated with significantly increased CD206+ macrophage tumor infiltration in the tumor core. These data suggest that mutations in these chromatin-modifying genes, including *SETD2*, *PBRM1*, and *KDM5C*, are associated with distinct immune infiltration patterns within the TIME and, thus, may influence the response to immunotherapy [54].

The observation that renal cell carcinoma (RCC) is a highly immune-infiltrated solid tumor [55] suggests that the major source of the "inflamed" TIME in RCC likely results from genomic changes distinct from TMB. One potential source could be mutations in chromatin-modifying genes, including *PBRM1* (mutated in about 60% of ccRCC), which result in conformational changes of the chromosome and thus allow for increased expression of key immune genes such as *IFNG* to mediate antitumor immune responses [56]. Mutation of *PBRM1* has not been consistently associated with clinical responses to ICIs [57].

One possible explanation for the lack of a consistent correlation between mutations of these chromatin-modifying genes (eg, *PBRM1* and *SETD2*) and clinical response could be due to the likelihood of these gene mutations generating mostly tumor-associated antigens (TAAs; ie, antigens that have elevated expression levels on cancer cells and also lower levels on host cells) instead of tumor-specific antigens (TSAs; ie, antigens found on cancer cells only). A supportive piece of evidence is the elegant pan-cancer analyses of the role of frameshift insertion and deletion mutations that can generate neoantigens to initiate antitumor immune responses in patients with kidney cancer, bladder cancer, prostate cancer, melanoma, and lung adenocarcinoma, [58].

Paradoxically, high immune infiltration in RCC correlates with poor outcomes [59]. Single-cell sequencing approaches identified enrichment of terminally exhausted CD8+ T cells and M2-like macrophages in advanced disease compared with early-stage disease, and these correlated with a poor prognosis [60]. In addition, the pretreatment TIME of ccRCC tumors that respond to ICI typically contains cytotoxic T cells expressing high levels of coinhibitory receptors and effector molecules. Finally, ccRCC cells divide into subpopulations differing in angiogenic signaling and upregulation of immunosuppressive programs after an ICI [61]. An analysis of the molecular characteristics of tumors from patients on the phase 2 IMmotion150 trials indicates that patients with a Teff^{high} gene signature (including T-effector presence and function, IFN-γ response, response to checkpoint inhibitors, high expression of PD-L1, and CD8+ T-cell infiltration) have better outcomes when treated with atezolizumab and bevacizumab, whereas those with a myeloid^{high} signature did poorly when treated with atezolizumab alone or in combination with bevacizumab [62]. Similarly, correlative research from the phase 3 JAVELIN Renal 101 clinical trial demonstrates that a 26-gene immunomodulatory signature (Renal-101 Immuno signature) is associated with longer progression-free survival in patients treated with avelumab plus axitinib [63]. Additional validation studies will be needed before these biomarkers can be used clinically.

Collectively, these findings from genomic analysis, TIME evaluation, and gene signature exploration suggest that a more detailed and advanced understanding of tumor-intrinsic factors (especially identification of TSAs that can generate antitumor immune responses) and tumor-extrinsic factors (especially how these factors modulate antitumor immune responses) in ccRCC is necessary not only to identify biomarkers to predict clinical response to immunotherapy, but also to develop novel and effective therapies for patients with ccRCC.

3.2.3. *Prostate cancer*

Prostate tumors exhibit somewhat distinct profiles of infiltrating immune cells [64,65]. Pretreatment prostate tumors are traditionally categorized as immunologically underactive with a relatively low TMB [66]. Some studies have noted high proportions of CD4+ and CD8+ T cells and FoxP3+ regulatory T cells in the prostate TIME [67]. This is more pronounced in tumors exhibiting PTEN tumor-suppressor protein loss [65]. Increased infiltration of T cells in the stromal regions, with higher proportions of CD4+ T cells than CD8+ T cells, correlated positively with PTEN protein loss in primary prostate tumors [41]. Another recent study revealed predominance of CD163+ macrophages in high-grade tumors [68]. Emerging reports have also demonstrated the distinct spatial profiles of T and B cells in germline homologous recombination repair deficient and sporadic prostate tumors with the presence of TLSs in the stromal regions [69]. Recently completed ICI trials have demonstrated the therapeutic impact on the prostate TIME [70]. Despite an underactive TIME, clinical responses were reported in patients harboring relatively higher TMBs or specific mutations in DDR genes [70]. In addition, in prostate cancer patients with a low TMB, those who can produce TAAs or TSAs to specifically generate antitumor immune responses also demonstrate favorable clinical outcomes in response to ICI (ipilimumab) therapy [66].

Overall, an understanding of the pretreatment TIME and genomic changes that lead to generation of antitumor immune responses will be key to provide insights into the biology of GU tumors and define precise biomarkers of therapeutic response, depending on the specific types of immunotherapy.

3.3. *Therapeutic immunomodulation in GU cancers*

Effective mucosal immune responses to organ-specific antigenic insults are best evoked by locally delivered immunomodulatory therapy. Despite its demonstrated efficacy, approximately 50% of patients have disease recurrence following intravesical BCG treatment of NMIBC [71]. Some studies have highlighted the inverse association between increased infiltration of regulatory T cells and CD163+ macrophages, and a poor response [72]. Adaptive immune resistance induced by increased levels of IFN-γ has been proposed as one of the factors underlying a poor response to BCG therapy [73]. It is tempting, however, to speculate

that BCG, an attenuated microbe, may not be able to activate immune cells in an exhausted bladder immune microenvironment [74], especially in cases of carcinoma in situ or patients nonresponsive to BCG who often exhibit high infiltration of immune cells and TLSs in pretreatment tumors [26]. A key finding from this study was the increased levels of tumor-derived DNA and immune exhaustion–related proteins such as PD-1, PD-L1, and CD70 in the post-BCG urine specimens of patients who exhibited high-grade recurrence.

For metastatic urothelial carcinoma, five immune checkpoint-inhibiting agents have been approved by the Food and Drug Association (FDA) as first-line, second-line, and adjuvant therapy. In the first-line setting, both atezolizumab (anti–PD-L1) and pembrolizumab (anti–PD-1) have been approved as the standard therapy for patients with advanced urothelial carcinoma, based on eligibility for first-line platinum-based chemotherapy and levels of tumor PD-L1 expression [75]. In addition, avelumab (anti–PD-L1) has been approved for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed following first-line platinum-containing chemotherapy [76]. Atezolizumab and durvalumab were later voluntarily withdrawn by the supporting companies due to follow-up phase 3 clinical trials in which these agents failed to meet primary survival endpoints. The failure of some of these agents (atezolizumab and durvalumab) in a specific clinical setting (first or second line after chemotherapy) begs the question of how to optimally target the bladder cancer TIME to maximize antitumor immune responses.

For patients with RCC, immune checkpoint–inhibiting agents have been approved by the FDA in the first-line, second-line, and adjuvant therapy settings. In the first-line setting, nivolumab plus ipilimumab (anti–CTLA-4), pembrolizumab plus axitinib (tyrosine kinase inhibitor), avelumab plus axitinib, nivolumab plus cabozantinib (tyrosine kinase inhibitor), and pembrolizumab plus lenvatinib (multitarget kinase inhibitor) have been approved [77–80]. In the adjuvant setting, pembrolizumab was recently shown to promote a significant improvement in disease-free survival after surgery in patients with RCC who were at a high risk of recurrence [81]. Together, some of these clinical successes demonstrate not only the well-founded strategy of targeting T cells in RCC for clinical benefit, but also potential combination approaches to optimize the RCC TIME to maximize antitumor immune responses.

In the USA, there are three approved immunotherapies for prostate cancer: sipuleucel-T and two anti–PD-1 antibodies (pembrolizumab and dostarlimab). Sipuleucel-T is a therapeutic vaccine targeting prostatic acid phosphatase, which is a TAA. A full treatment regimen includes infusion of sipuleucel-T three times at approximately 2-wk intervals. Guidelines suggest that sipuleucel-T should be offered to men with less aggressive disease who are asymptomatic or minimally symptomatic [82–84].

Pembrolizumab and dostarlimab are approved in a tumor-agnostic fashion that applies to a small subset of patients with metastatic castration-resistant prostate cancer (mCRPC) [85]. Roughly 5% of men with mCRPC are

Table 1 – FDA approved immune checkpoint inhibitors in GU cancers

Cancer type	ICI therapy	Trial	Phase	Target	Line of treatment
Urothelial carcinoma	Atezolizumab [102]	IMVIGOR-210	II	PD-L1	First line (platinum-ineligible patients)/second line
	Pembrolizumab [102]	KEYNOTE-052	II	PD-1	First line (platinum-ineligible patients)/second line
	Avelumab [102]	JAVELIN Bladder-100	III	PD-L1	Maintenance therapy
	Nivolumab [102]	CheckMate-275	II	PD-1	Second line
	Durvalumab [102]	Study-1108	I/II	PD-L1	Second line
Prostate cancer	Pembrolizumab [103]	KEYNOTE -199	II	PD-1	Treatment-refractory metastatic castration-resistant prostate cancer
Renal cell carcinoma	Nivolumab + ipilimumab [104]	CheckMate-214	III	PD-1 + CTLA-4	First line
	Pembrolizumab + axitinib [104]	KEYNOTE-426	III	PD-1 + tyrosine kinase receptor (VEGFR-1,2,3)	First line
	Avelumab + axitinib [104]	JAVELIN 101	III	PD-L1 + tyrosine kinase receptor (VEGFR-1,2,3)	First line
	Nivolumab + cabozantinib [79]	CheckMate 9ER	III	PD-1 + tyrosine kinase receptor (c-MET, AXL, RET, and VEGFR2)	First line
	Pembrolizumab + lenvatinib [80]	KEYNOTE-775	III	PD-L1 + multitarget kinase inhibitor	First line
	Nivolumab [105]	CheckMate 025	III	PD-1	Second line
	Pembrolizumab [106]	KEYNOTE-564	III	PD-1	Adjuvant

FDA = Food and Drug Association; GU = genitourinary; ICI = immune checkpoint inhibitor.

microsatellite instability (MSI) high and about 5% are TMB high, which may overlap significantly [86,87]. The response rate for biomarker-positive men treated with pembrolizumab is about 50%, and these responses are often durable [86,87]. Dostarlimab is also approved for MSI-high solid tumors including mCRPC. Beyond these limited indications, ICIs have not been proved to be efficacious in prostate cancer. This lack of response can largely be attributed to both noninflamed TIME and increased infiltration by immunosuppressive cell subsets [64,65,88,89]. Currently approved ICIs in GU cancers are summarized in Table 1.

3.4. Emerging role of TLSs as biomarkers in GU tumors

Tumor-infiltrating B cells localized within or outside of TLSs are associated with favorable prognosis and response to ICIs in some GU cancers [27,28,90–92]. A comparison of TLSs in ccRCC and MIBC revealed their presence to be associated with poor outcomes only in RCC [29]. However, TLSs were observed more frequently in high-grade ccRCC and bladder cancer, suggesting the presence of exhausted immune cells within TLSs due to the chronic nature of the disease. The overall abundance of TLSs is higher in pretreatment tumors from patients with MIBC than in those from patients with NMIBC [23,93]. These patients showed improved survival following adjuvant chemotherapy and an ICI [92,94–96]. Given the ability of BCG to induce the formation of granulomas that are often associated with decreased disease recurrence [97], it is reasonable to suspect that TLS-formed post-tumor resection would be associated with similarly positive clinical outcomes. However, some studies have demonstrated a variable association between BCG-induced granulomas and response [98]. Much is still unknown regarding the specific treatment type associated with the predictive relevance of TLSs.

4. Conclusions

While some immunomodulatory therapies reduce the rates of recurrence and restrict disease progression, the lack of a memory response induced by exogenously activating immune responses or "releasing the brakes" on immune checkpoints does not always achieve beneficial therapeutic outcomes. Clinical usefulness of predictive biomarkers such as immune cell infiltration, immune checkpoint expression, TMB, and DDR status is yet to be proved. Challenges associated with clinical translation include tumor heterogeneity, immune-related adverse events, and other patient factors such as age and sex [99]. However, ongoing trials evaluating variable therapeutic sequencing of immunomodulatory treatments may lead to improvement in favorable outcomes. An understanding of the role of cancer-associated fibroblasts in GU cancer is beginning to emerge [100] and presents an attractive avenue for therapeutic modulation. Immune cell therapy with gene-edited chimeric antigen receptor–engineered autologous T cells or natural killer cells combined with an ICI and/or chemotherapy may prove promising [101].

Overall, our understanding of the pre- and post-treatment immunological events that evolve from crosstalk between tumor intrinsic alterations and host immune responses has increased substantially over the past decade, with a more finessed understanding of immunobiology in general and a concerted effort to explore these concepts in GU malignancy.

Author contributions: Madhuri Koti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Koti, Gao.
Acquisition of data: Koti, Gao, Gulley, Ingersoll, Galsky.
Analysis and interpretation of data: Koti, Gao, Gulley, Ingersoll, Galsky, Cathomen.
Drafting of the manuscript: Koti, Gao, Gulley, Ingersoll, Galsky, Cathomen.
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