

Immune Checkpoint Inhibitor Resistance in Genitourinary Cancers: Mechanisms, Biomarkers, and Emerging Therapeutic Strategies

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Immune checkpoint inhibitors (ICI) targeting the programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) axes have transformed the treatment landscape of genitourinary (GU) malignancies, yielding durable responses in subsets of patients with urothelial carcinoma, renal cell carcinoma (RCC), and selected cases of metastatic castration-resistant prostate cancer (mCRPC). However, most patients exhibit primary resistance, and those who initially respond frequently develop acquired resistance, substantially limiting long-term clinical benefit. A systematic understanding of the biological mechanisms driving resistance, the identification of robust predictive biomarkers, and the design of rational combination strategies are essential to extend the therapeutic reach of ICI-based regimens. To address this need, an integrative review was conducted following the Whitemore and Knafl (2005) framework. Systematic searches were performed in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Embase, and Web of Science, covering the period January 2020 to April 2026. Studies were selected according to predefined inclusion criteria encompassing original research, clinical trials, systematic reviews, and narrative reviews reporting on resistance mechanisms, predictive biomarkers, or emerging therapeutic strategies for ICI in GU cancers. A total of 32 studies met eligibility criteria. Three interconnected resistance categories were identified: (1) tumor cell-intrinsic mechanisms, including low tumor mutational burden (TMB), loss of antigen presentation via major histocompatibility complex class I (MHC-I) downregulation, activation of the Wnt/ β -catenin and JAK/STAT pathways, and epigenetic reprogramming; (2) tumor microenvironment (TME)-mediated immunosuppression, driven by myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), cancer-associated fibroblasts (CAFs), and immunosuppressive cytokines including TGF- β and vascular endothelial growth factor (VEGF); and (3) acquired post-treatment resistance involving T-cell exhaustion and upregulation of alternative immune checkpoints. Among validated or clinically used biomarkers, PD-L1 expression demonstrated variable predictive utility across GU cancer types, while TMB-high status (≥ 10 mutations/megabase) predicted improved response to pembrolizumab across solid tumors. Emerging therapeutic strategies include ICI plus tyrosine kinase inhibitor (TKI) combinations, antibody-drug conjugates (ADCs), MDSC-targeted interventions, therapeutic vaccines, and radiotherapy sensitization. Overall, ICI resistance in GU cancers emerges as a multidimensional phenomenon with distinct biological drivers across tumor subtypes; precision combinations targeting both intrinsic tumor factors and the immunosuppressive TME represent the most promising avenue to overcome resistance, and standardization of composite biomarker platforms is urgently needed to individualize ICI selection in clinical practice.

Keywords: ICI; resistance; genitourinary cancers; tumor microenvironment; biomarkers; PD-L1; tumor mutational burden; urothelial carcinoma; renal cell carcinoma; prostate cancer; antibody-drug conjugates; therapeutic strategies

Introduction

Immune checkpoint inhibitors (ICI) have emerged as a cornerstone of oncologic therapy, fundamentally altering the prognosis of patients with advanced malignancies. In the domain of genitourinary cancers, agents targeting the programmed cell death protein-1 (PD-1), its ligand and programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4) have achieved regulatory approval across multiple indications, including locally ad-

vanced and metastatic urothelial carcinoma, advanced renal cell carcinoma (RCC), and a biomarker-selected subset of metastatic castration-resistant prostate cancer (mCRPC) [1,2]. These approvals reflect the capacity of ICI therapy to generate durable clinical responses—including complete remissions—in a proportion of patients who would otherwise face a uniformly poor prognosis under conventional cytotoxic regimens.

Despite this progress, the overall clinical benefit of ICI monotherapy remains heterogeneous and frequently

limited. In the pivotal CheckMate 275 trial, nivolumab achieved an objective response rate (ORR) of 19.6% (95% confidence interval [CI]: 15.0–24.9%) in patients with platinum-resistant metastatic urothelial carcinoma, with a median overall survival of 8.7 months [3]. These figures encapsulate the central clinical challenge: while a subset of patients derives transformative benefit, the majority experience primary resistance or short-lived responses followed by disease progression [4,5]. In mCRPC, the immunologically cold phenotype of prostate tumors has restricted ICI efficacy to patients harboring high microsatellite instability, deficient mismatch repair, or high tumor mutational burden (TMB), with pembrolizumab representing the only ICI currently approved in this setting [2,6].

The mechanisms underlying ICI resistance are multifaceted, operating at the level of the tumor cell, the tumor microenvironment (TME), and the systemic immune landscape. Primary resistance reflects pre-existing biological features that prevent adequate anti-tumor immune activation, whereas acquired resistance emerges after an initial response through adaptive immunological and genomic changes [7]. Understanding these mechanisms is not merely an academic exercise; it provides the rational basis for designing combination strategies capable of expanding the population of patients who benefit from immunotherapy [8,9].

Concurrently, the identification of predictive biomarkers capable of prospectively stratifying patients by their likelihood of response has become a research priority of the highest order. PD-L1 expression by immunohistochemistry (IHC), while incorporated into regulatory approvals, demonstrates inconsistent predictive value across genitourinary (GU) tumor types [10,11]. TMB has gained traction as a tumor-agnostic biomarker, yet substantial histology-specific variation limits its universal applicability [12]. Novel candidate biomarkers—including *APOBEC3B* mutational signatures, major histocompatibility complex class I (MHC-I) expression, neoantigen clonality, and immune gene expression profiles—are under active investigation [13].

This integrative review synthesizes the current evidence on resistance mechanisms, predictive biomarkers, and emerging therapeutic strategies for ICI-based treatment in GU cancers. The objective is to provide a comprehensive, structured framework to guide clinical decision-making and to identify the most promising avenues for future investigation.

Materials and Methods

Study Design: Integrative Review Framework

This study was conducted as an integrative review following the methodological framework proposed by Whittemore and Knafl [14]. This approach enables the inclusion of diverse study designs—experimental, quasi-experimental,

and non-experimental—and is therefore particularly suited to synthesizing a literature base that encompasses clinical trials, observational studies, translational research, and systematic reviews. The integrative design permits a comprehensive analysis of the existing body of evidence without restricting the corpus to randomized studies alone, thereby reflecting the full complexity of the scientific landscape on ICI resistance in GU malignancies.

Search Strategy and Data Sources

Systematic literature searches were conducted in four primary databases: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Embase, and Web of Science. The search period covered January 2020 through April 2026, capturing evidence generated after the initial wave of ICI approvals in GU cancers and including the most recent developments in resistance mechanisms and emerging therapies. This window was selected because ICI resistance as a distinct area of mechanistic and clinical investigation accumulated predominantly after the initial regulatory approvals of ICI agents in urothelial carcinoma, RCC, and mCRPC (2016–2019); earlier landmark trials establishing baseline ICI efficacy in these tumors (e.g., CheckMate 275 [3]) are referenced as foundational context in the Introduction but fall outside the formal evidence-synthesis window.

The search strategy combined controlled vocabulary terms, when available, with free-text terms related to three core concepts: immune checkpoint inhibition, resistance or non-response, and genitourinary malignancies. Additional terms were included to capture biomarker studies, tumor microenvironment-mediated immunosuppression, and therapeutic strategies intended to overcome immune checkpoint inhibitor resistance. The search strategy was adapted to the syntax and indexing structure of each database. The complete database-specific search strings are presented in **Supplementary Table 1**.

In brief, the PubMed/MEDLINE strategy combined MeSH terms and title/abstract terms for immune checkpoint inhibitors, PD-1, PD-L1, CTLA-4, resistance, biomarkers, tumor microenvironment, urothelial carcinoma, bladder cancer, renal cell carcinoma, kidney cancer, prostate cancer, and genitourinary neoplasms. Equivalent Emtree terms and free-text fields were used in Embase; CENTRAL was searched using title, abstract, and keyword fields; and Web of Science was searched using topic fields. Search results were exported from each database and imported into reference-management software for deduplication before title and abstract screening.

Inclusion and Exclusion Criteria

Studies were included if they: (1) addressed mechanisms of primary or acquired resistance to ICI therapy; (2) reported on predictive biomarkers for ICI response or resistance in at least one GU cancer type (urothelial carcinoma, RCC, or prostate cancer); (3) evaluated emerging therapeutic

tic strategies to overcome ICI resistance; (4) were published in peer-reviewed journals between 2020 and 2026; and (5) were available in English. Narrative and integrative reviews were eligible for inclusion because, for several resistance mechanisms and biomarkers addressed in this synthesis, dedicated primary research in genitourinary tumor types remains sparse; such reviews often aggregate translational and mechanistic findings — frequently derived from pan-cancer cohorts — that have not yet been replicated in GU-specific primary studies. Their inclusion is treated as a secondary evidentiary tier, explicitly distinguished from primary clinical/translational findings in the Results and Discussion sections.

Studies were excluded if they: (1) were limited to non-GU tumor types without providing GU-relevant analyses or mechanistic insights transferable to the GU context; (2) were case reports lacking substantive mechanistic, *ex vivo*, or cross-case analytical data; (3) were conference abstracts, editorials, or letters without sufficient methodological detail; or (4) were preprints without peer review.

Study Selection and Data Extraction

Following duplicate removal, titles and abstracts were screened for eligibility. Full texts of potentially eligible records were retrieved and assessed against the predefined inclusion criteria. Data were extracted systematically, encompassing study design, cancer type, patient population or sample characteristics, ICI agent(s) investigated, resistance mechanisms described, biomarkers evaluated, therapeutic strategies proposed, and key numerical findings.

Quality Assessment

Given the integrative nature of this review and the substantial heterogeneity of the included evidence, which comprised primary observational and translational studies as well as narrative and systematic reviews, no single formal risk-of-bias instrument was applied across the entire evidence base. Instead, evidence was interpreted according to study design, directness to genitourinary malignancies, and whether findings originated from primary or secondary sources.

Results

Search Results and Study Characteristics

The systematic search across the four primary databases identified 118 records. Following deduplication, 95 unique records were screened. After title and abstract review, 45 records were excluded for failing to address ICI resistance mechanisms, biomarkers, or therapeutic strategies in GU tumors leaving 50 reports sought for retrieval (all 50 were successfully retrieved). These 50 reports were assessed for eligibility, of which 18 were subsequently excluded for the following reasons: non-GU focus without transferable mechanistic content ($n = 9$), exclusive case re-

port design without cross-case synthesis ($n = 4$), conference abstract or non-peer-reviewed format ($n = 3$), and insufficient methodological detail ($n = 2$). Accordingly, 32 studies met eligibility criteria and were included in the final synthesis (Fig. 1).

Among the 32 included sources, narrative and integrative reviews constituted the majority of included sources ($n = 20$; 62.5%), followed by original research articles ($n = 10$; 31.3%), one case report/*ex vivo* study ($n = 1$; 3.1%), and one case series ($n = 1$; 3.1%). Urothelial carcinoma was discussed in 20 included sources (62.5%), followed by RCC (43.8%) and prostate cancer (25.0%); 31.3% of studies addressed multiple GU malignancies simultaneously. Among the evaluated ICI strategies discussed across the included sources, PD-1 inhibitors were the most frequently represented, particularly pembrolizumab and nivolumab. The general characteristics of the included studies are summarized in Table 1.

Tumor Cell-Intrinsic Mechanisms of Resistance

Tumor cell-intrinsic resistance arises from molecular and genomic features that limit immune recognition independent of microenvironmental factors. As synthesized in narrative reviews addressing multiple solid tumor types rather than genitourinary cancers specifically, tumors with a paucity of somatic mutations generate insufficient neoantigens to trigger effective T-cell recognition, thereby precluding productive anti-tumor immune responses [4,12]. However, the relevance of this mechanism to GU malignancies remains to be directly validated in GU-specific studies. Prostate cancer epitomizes this paradigm: as discussed in narrative reviews focused specifically on genitourinary and prostate cancer biology, this tumor type typically harbors a low mutational load that contributes to its immunologically cold phenotype and the historically limited efficacy of ICI in unselected populations [2,15].

Downregulation of antigen presentation machinery, particularly MHC class I expression, represents a second critical intrinsic resistance mechanism. As described in narrative reviews of resistance mechanisms across solid tumors rather than genitourinary cancers specifically, loss-of-function mutations or epigenetic silencing of beta-2-microglobulin (B2M) or HLA genes impairs the surface display of tumor-derived peptides, rendering tumor cells invisible to cytotoxic CD8⁺ T cells regardless of their neoantigen burden [7,9]; however, the relevance of this mechanism to GU malignancies remains to be directly validated in GU-specific studies. In urothelial carcinoma specifically, MHC-I downregulation has been documented in patients progressing on PD-1/PD-L1 blockade, and MHC-I pathway integrity has emerged as a candidate predictive biomarker [16].

Activation of oncogenic signaling pathways provides an additional layer of intrinsic resistance. As synthesized in a narrative review of ICI resistance mechanisms across

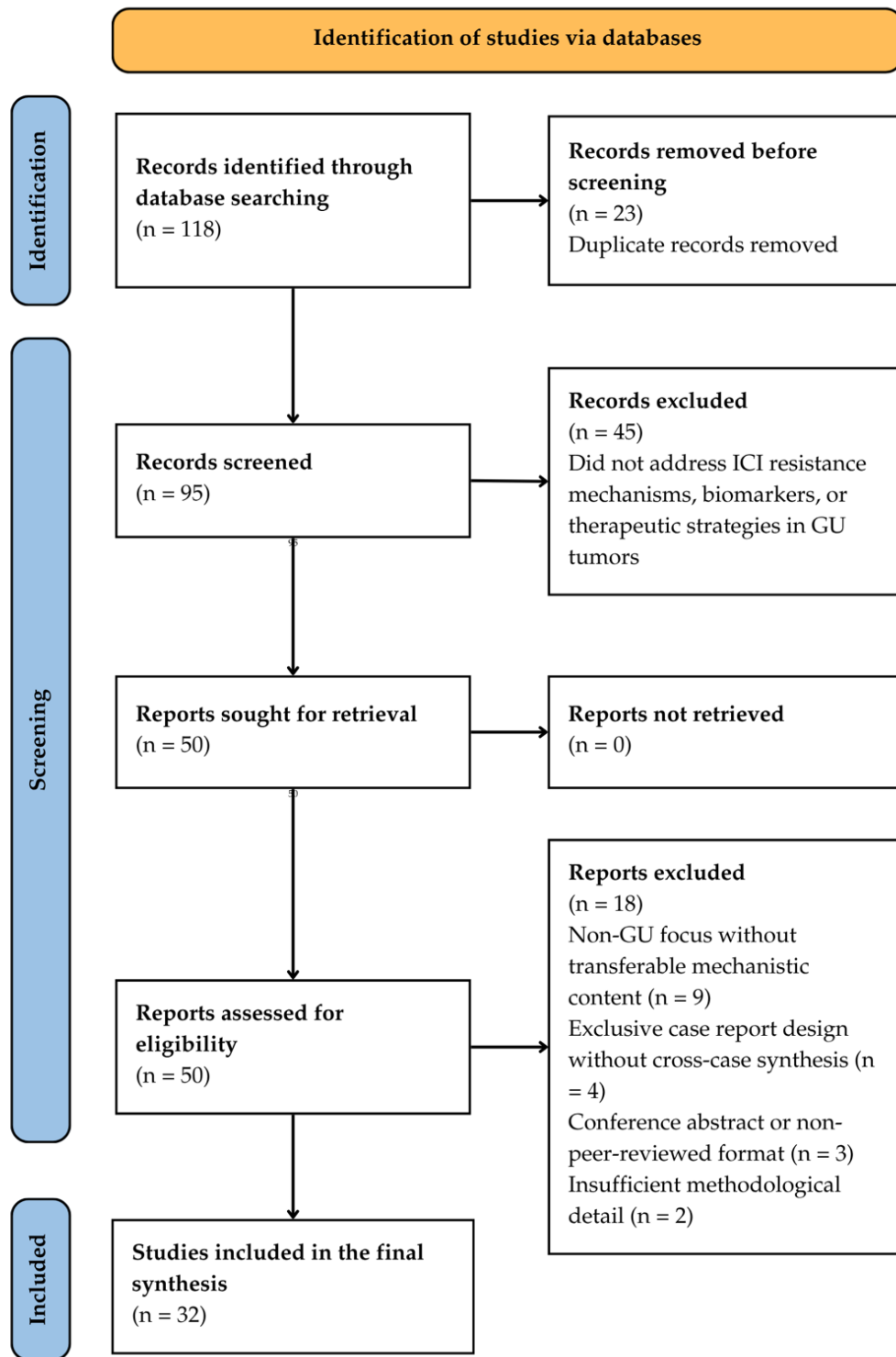


Fig. 1. PRISMA flow diagram of the literature search and study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

solid tumors, the Wnt/ β -catenin pathway suppresses the expression of CCL4, a chemokine required for intratumoral recruitment of dendritic cells and CD8⁺ T cells, thereby generating an immune-excluded or immune-desert tumor phenotype [17]. This pathway was characterized in studies

spanning multiple solid tumor types rather than genitourinary cancers specifically; evidence for this mechanism in GU tumor resistance remains inferential and requires GU-specific mechanistic confirmation. Similarly, as described in narrative reviews of ICI resistance mechanisms across

Table 1. General characteristics of the 32 included studies.

Characteristic	n (%)	Detail/Range
Number of included studies	32	—
Study design		
Narrative/integrative review	20 (62.5%)	—
Original research article	10 (31.3%)	—
Case report/ <i>ex vivo</i> study	1 (3.1%)	—
Case series	1 (3.1%)	—
Publication period		
2020	6 (18.8%)	—
2021	7 (21.9%)	—
2022	4 (12.5%)	—
2023	9 (28.1%)	—
2024	5 (15.6%)	—
2025	1 (3.1%)	—
Cancer entities represented in included studies (non-exclusive)		
Urothelial carcinoma (bladder)	20 (62.5%)	Most represented tumor type
Renal cell carcinoma	14 (43.8%)	Predominantly clear-cell subtype
Prostate cancer (mCRPC)	8 (25.0%)	Including androgen-resistant phenotype
Multiple GU malignancies	10 (31.3%)	Cross-tumor comparisons

mCRPC, metastatic castration-resistant prostate cancer; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen-4.

solid tumors, JAK1/JAK2 mutations, identified in patients with acquired resistance to PD-1 blockade, ablate IFN- γ signaling and disrupt downstream antigen presentation up-regulation, undermining the immunostimulatory effect of ICI [4,7]; this mechanism's relevance to GU malignancies likewise remains to be directly validated in GU-specific studies.

Epigenetic reprogramming constitutes a particularly dynamic and therapeutically tractable resistance mechanism. As discussed in a GU-focused narrative review, promoter hypermethylation of immune-related gene loci, altered histone acetylation patterns, and dysregulation of non-coding RNA networks — including long non-coding RNAs (lncRNAs) and microRNAs — have been shown to reshape the immunological phenotype of GU tumors and promote immune evasion [18]; a complementary narrative review spanning multiple solid tumor types supports the broader epigenetic-mechanism rationale, though its applicability beyond the tumor types it directly studied should be regarded as indirect evidence [19]. In bladder and renal cancers specifically, the same GU-focused review describes lncRNAs regulating drug resistance pathways across multiple therapeutic contexts [19], and a narrative review addressing multiple cancer types including GU malignancies further implicates immune-related lncRNAs in the modulation of T-cell-mediated immune responses and immunosuppressive TME remodeling, positioning lncRNA-mediated epigenetic reprogramming as a combinatorial target for overcoming ICI resistance — a synthesis that should likewise be read as indirect evidence where it extends beyond GU-specific findings [20].

Tumor Microenvironment-Mediated Immunosuppression

The TME of GU cancers is characterized by a complex network of immunosuppressive cellular and soluble components that attenuate anti-tumor immune responses and confer resistance to ICI therapy. Myeloid-derived suppressor cells (MDSCs)—encompassing granulocytic (G-MDSCs) and monocytic (M-MDSCs) subpopulations—are prominently expanded in the TME of urothelial carcinoma and RCC. As described in narrative reviews addressing immunosuppressive cell populations across solid tumors generally, MDSCs exert their immunosuppressive effects through multiple non-redundant mechanisms, including the production of reactive oxygen species, arginase-1, nitric oxide synthase, and TGF- β , which collectively suppress CD8⁺ T-cell function and promote Treg differentiation [21,22]; this mechanism has not yet been directly validated in GU-specific studies. Elevated MDSC infiltration has been associated with reduced response to ICI in both bladder and renal cancers, and high levels of PD-L1⁺ MDSCs identified in RCC tumor specimens suggest that this cellular compartment contributes to dual immunosuppression by simultaneously impairing T-cell activity and engaging the PD-1/PD-L1 axis [23,24]. In preclinical bladder cancer models, gemcitabine-mediated MDSC depletion significantly enhanced the efficacy of adoptive T-cell transfer, confirming the therapeutic relevance of this target [25].

Tregs represent a second major immunosuppressive cellular component of the GU tumor immune microenvironment. As described in the same general reviews of immunosuppressive cell populations across solid tu-

mors cited above, Tregs suppress effector T-cell activation through CTLA-4-mediated downregulation of co-stimulatory molecule expression on antigen-presenting cells, secretion of IL-10 and TGF- β , and consumption of IL-2 in the local environment [21,22]; as before, this should be regarded as indirect evidence for GU tumors specifically. In clear-cell RCC (ccRCC), the ratio of Tregs to cytotoxic T cells — reported in a primary prognostic-signature study and further synthesized in a ccRCC-focused narrative review — represents a prognostic and potentially predictive variable for ICI response [23,26].

Cancer-associated fibroblasts (CAFs) contribute to physical and biochemical barriers to immune infiltration. As discussed in a ccRCC-focused narrative review, CAF subpopulations in ccRCC are characterized by diverse functional states — including myofibroblastic, inflammatory, and immunosuppressive phenotypes — that create a stromal barrier that impedes effector T-cell trafficking into tumor parenchyma while actively secreting vascular endothelial growth factor (VEGF) and TGF- β [26]; the contribution of CAF-derived VEGF and TGF- β to this barrier is further supported by a general review of vascular-immune crosstalk in cancer, whose applicability to GU-specific CAF biology should be regarded as indirect evidence pending direct confirmation [27]. The interplay between CAFs, tumor vasculature, and immune cell exclusion constitutes a therapeutically important axis for overcoming the immunologically cold phenotype observed in certain GU tumor subtypes.

Androgen signaling imparts a distinctive immunosuppressive signature in prostate cancer. Androgen receptor (AR) activation promotes the recruitment of MDSCs and M2-polarized tumor-associated macrophages (TAMs), while androgen deprivation therapy paradoxically induces an initial inflammatory response that is subsequently counteracted by adaptive immunosuppressive remodeling of the TME [28]. This androgen-driven immunosuppression compounds the low-TMB, antigen-poor substrate described in Tumor Cell-Intrinsic Mechanisms of Resistance, producing a dual-layer resistance phenotype in which both insufficient tumor antigenicity and active immunosuppressive remodeling must be overcome simultaneously — in contrast to urothelial carcinoma and RCC, where intrinsic antigenicity is comparatively preserved and resistance is more microenvironment-dominant. This compound phenotype helps explain the historically limited efficacy of ICI monotherapy in unselected mCRPC populations relative to urothelial carcinoma and RCC, and underscores why combination strategies pairing androgen-axis modulation with immune-activating approaches (Emerging Therapeutic Strategies to Overcome Resistance) are particularly mechanistically motivated in this tumor type. *STAT3* activation in tumor-associated antigen-presenting cells has been identified as an additional immunosuppressive node

in both renal and bladder cancer, functioning as a convergence point for multiple upstream immunosuppressive signals [29].

Acquired Resistance and Alternative Checkpoint Upregulation

Acquired resistance to ICI therapy is characterized by the progressive erosion of initially effective anti-tumor immune responses. T-cell exhaustion, mediated by chronic antigen stimulation, results in the transcriptional and epigenetic reprogramming of tumor-specific T cells toward a dysfunctional state marked by co-expression of multiple inhibitory receptors—including lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and TIGIT—that diminishes cytolytic capacity and proliferative potential, rendering cells unresponsive to further PD-1 blockade [30]. This trajectory reflects a hierarchical exhaustion program: precursor exhausted T cells retain partial proliferative and effector capacity and can be transiently reinvigorated by PD-1 blockade, whereas progression to a terminally exhausted state — fixed by durable epigenetic remodeling rather than reversible transcriptional silencing — renders cells refractory to checkpoint blockade regardless of further pathway inhibition [30]. Acquired resistance to ICI therapy can therefore be understood, at least in part, as the clinical manifestation of this precursor-to-terminal exhaustion transition occurring under sustained antigenic and inhibitory-receptor signaling pressure during treatment.

Upregulation of alternative immune checkpoint molecules represents a key adaptive resistance strategy whereby tumors preserve immune evasion despite initial PD-1/PD-L1 pathway blockade. LAG-3 and TIM-3 are among the most clinically relevant compensatory checkpoints in GU tumors. As synthesized in narrative reviews of checkpoint-blockade resistance, their co-expression with PD-1 on exhausted tumor-infiltrating lymphocytes has been documented in urothelial carcinoma and RCC, and their inhibition constitutes one of the most actively pursued strategies for re-sensitizing tumors to checkpoint blockade [5,9]. As discussed in a pan-cancer perspective on tumor mutational burden and immunotherapy response, tumor immunological heterogeneity—encompassing both spatial and temporal variability in antigen expression and immune infiltration—further complicates the maintenance of durable responses [12]. The magnitude of this effect in GU malignancies remains to be established in GU-specific studies.

Neoantigen clonality has been proposed as a refined predictor of ICI response in urothelial cancers. Tumors with a dominant clonal neoantigen architecture are more likely to sustain T-cell responses, while those with high subclonal heterogeneity may evade immune recognition through selective clonal outgrowth of antigen-negative tumor cells [31]. As described in a pan-cancer review of predictive

biomarkers and resistance mechanisms, the mismatch repair (MMR) system exerts a bidirectional influence: MMR-deficient tumors typically harbor high TMB and respond favorably to PD-1 blockade, while MMR-proficient tumors with an immune-desert phenotype exhibit a particularly unfavorable immunotherapy profile [32]. Its applicability to GU tumors remains to be established by dedicated GU-focused studies.

Taken together, the resistance landscape differs meaningfully across GU tumor types. Urothelial carcinoma resistance is shaped predominantly by antigen-presentation defects (MHC-I downregulation [16]) and compensatory checkpoint upregulation (LAG-3/TIM-3 co-expression [5,9]), occurring against a comparatively immunogenic background. RCC resistance is dominated by tumor microenvironment immunosuppression — MDSC and Treg infiltration, CAF-mediated stromal exclusion, and VEGF-driven vascular dysfunction [21,22,23,24,25,26,27] — rather than by intrinsic antigenicity deficits. Prostate cancer exhibits the most pronounced intrinsically cold phenotype, driven by low TMB and androgen-receptor-mediated immunosuppressive remodeling (Tumor Microenvironment-Mediated Immunosuppression); this tumor type is also the least represented in the available evidence base (8/32 included studies, 25.0%), which constrains the granularity of prostate-specific conclusions relative to urothelial carcinoma and RCC.

Predictive Biomarkers

The validation of reliable predictive biomarkers for ICI response in GU malignancies has been a principal focus of translational oncology research.

Protein and Immunohistochemical Biomarkers

PD-L1 expression, measured by IHC, remains the most extensively evaluated biomarker and is incorporated into the regulatory approval label for several ICI indications. As synthesized in a urothelial-carcinoma-focused narrative review and supported by primary cohort data, its predictive utility is inconsistent across GU cancer subtypes: in urothelial carcinoma, PD-L1 positivity correlates with higher ORRs in some but not all clinical trials, and its performance differs depending on the antibody clone, scoring algorithm (tumor proportion score vs. combined positive score), and timing of assessment relative to prior therapy [10,33]. The genomic and clinicopathological characterization of PD-L1-positive urothelial carcinomas has revealed co-occurring features — including APOBEC mutagenesis, high TMB, and immune-inflamed molecular subtypes — that may contribute more meaningfully to the prediction of ICI benefit than PD-L1 expression alone [13].

Genomic Biomarkers

TMB has been validated as a predictive biomarker in the KEYNOTE-158 study, where participants with TMB

≥ 175 mutations/exome achieved an ORR of 31.4% with pembrolizumab compared to 9.5% among those with TMB below this threshold; however, KEYNOTE-158 was a pan-tumor basket trial rather than a GU-specific study, and this finding should be regarded as indirect evidence for GU malignancies [34]. The FDA approval of pembrolizumab for TMB-high (≥ 10 mutations/megabase) solid tumors established the first tumor-agnostic biomarker-driven indication for an ICI, though the optimal threshold remains tumor-type dependent; this tumor-agnostic indication likewise rests on pan-cancer rather than GU-specific data [12,35]. In GU cancers specifically, high TMB in nivolumab-treated urothelial carcinoma patients (defined as ≥ 170 mutations per tumor in an exploratory quartile-based analysis) was associated with improved ORR, progression-free survival, and overall survival in the CheckMate 275 analysis, with consistent benefit observed regardless of baseline PD-L1 expression level [36] — a GU-specific primary finding that anchors the broader TMB rationale described above.

Beyond TMB, genomic biomarkers under active investigation in GU cancers include APOBEC3B mutational signatures, which have been associated with enhanced immunogenicity in urothelial carcinoma and may inform response to PD-L1 blockade in combination with CD274 expression patterns [13]; neoantigen clonality, which captures the proportion of mutations present in all tumor clones and provides a more refined measure of immunogenic antigenicity than TMB alone [31]; MHC-I pathway integrity, including HLA-I expression and B2M status, which predicts the capacity for neoantigen presentation and T-cell recognition [16]; and POLQ (DNA polymerase theta), identified as a marker of a better-responding immunotherapy subset in muscle-invasive bladder cancer with high PD-L1 expression [37].

Transcriptomic and Gene Expression Biomarkers

Composite immune gene expression signatures, including the 18-gene tumor inflammation signature and interferon- γ gene expression profiles, have also been proposed as predictive tools, based on a cohort that included both GU and non-GU (NSCLC) patients [38]. Machine learning approaches applied to transcriptomic data across urothelial carcinoma and RCC patients specifically have further revealed that no single baseline transcriptional signature reliably predicts response to PD-L1 blockade across histologies, highlighting significant inter-tumor heterogeneity and the need for histology-specific, composite biomarker panels [38].

Immune Cell-Based and Emerging Systemic Biomarkers

Beyond tumor-intrinsic markers, cellular composition of the immune microenvironment has itself been proposed as predictive of ICI response. The ratio of regulatory to cytotoxic T cells in clear-cell RCC has been identified as a prognostic and potentially predictive variable for

ICI response, reported in a primary prognostic-signature study and further synthesized in a ccRCC-focused narrative review (Tumor Microenvironment-Mediated Immunosuppression) [23,26], and PD-L1-expressing myeloid-derived suppressor cell density in RCC tumor specimens has similarly been associated with immunotherapy outcome [24]. As discussed in a bladder-cancer-focused narrative review, the role of the microbiome as a systemic immune modulator is also emerging as a relevant biological determinant of ICI response in bladder cancer [39]. However, none of these immune cell-based metrics has yet been validated prospectively as a stand-alone predictive biomarker in genitourinary cancers, and their clinical applicability remains contingent on standardization of quantification methods across studies.

Cross-Cutting Limitations of Biomarker Assessment

Several methodological factors limit the comparability and clinical applicability of the biomarkers discussed above. PD-L1 IHC results vary according to antibody clone and scoring algorithm (tumor proportion score versus combined positive score), as noted, but are further confounded by intratumoral and intertumoral heterogeneity of expression, the timing of biopsy relative to prior systemic therapy, and the choice of tissue versus liquid biopsy material — circulating biomarkers offer more frequent, less invasive sampling but have not been consistently validated against tissue-based reference standards in GU cancers. Prior treatment exposure, particularly platinum-based chemotherapy or androgen-deprivation therapy in prostate cancer, can independently remodel the tumor immune microenvironment, confounding biomarker assessments obtained from archival rather than fresh, treatment-contemporaneous tissue. These factors collectively constrain direct comparison of biomarker performance across the studies synthesized in this review and should inform the design of future GU-specific validation studies.

Emerging Therapeutic Strategies to Overcome Resistance

Currently Approved and Guideline-Embedded

The co-administration of ICI with VEGF-targeted tyrosine kinase inhibitors (TKIs) represents the most clinically advanced approach to overcoming ICI resistance in GU cancers. VEGF signaling promotes TME immunosuppression through endothelial cell dysfunction, impaired T-cell trafficking, and MDSC accumulation; its pharmacological inhibition thereby enhances immune infiltration and ICI efficacy [40]. In RCC and advanced urothelial carcinoma, ICI plus TKI combinations have demonstrated substantially improved outcomes compared to TKI monotherapy, with VEGFR-targeted agents including cabozantinib, lenvatinib, and axitinib serving as complementary partners to anti-PD-1 or anti-PD-L1 antibodies, as summarized in GU-focused reviews of this combination strategy [41,42].

Approved (Enfortumab Vedotin) and Late-Phase Investigational (Disitamab Vedotin)

Antibody-drug conjugates (ADCs) have emerged as a transformative modality for patients with ICI-refractory GU tumors. Enfortumab vedotin, targeting nectin-4 on urothelial carcinoma cells, has achieved regulatory approvals based on compelling efficacy data in platinum- and ICI-pretreated populations. The phase II evaluation of disitamab vedotin demonstrated an ORR of 50% in human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic urothelial carcinoma patients across two combined phase II trials, supporting its role as a next-generation option for ICI-resistant disease [43]. Nectin-4 and PD-L1 co-expression patterns in bladder cancer further inform the rational selection of ADC plus ICI combination strategies, as discussed in a urothelial-carcinoma-focused review and a primary genomic characterization study [41,44]. From a clinical decision-making perspective, selection among these agents can be informed by target expression and treatment sequencing: disitamab vedotin's mechanism specifically depends on HER2 positivity, making HER2 testing a rational first step before considering this option; for currently approved ADC therapy, enfortumab vedotin remains the relevant option in this setting, whereas sacituzumab govitecan should be regarded in the context of prior clinical evidence rather than as a currently approved treatment option for urothelial carcinoma.

Preclinical Stage

MDSC-targeted therapeutic strategies constitute a mechanistically grounded approach to reprogramming the immunosuppressive TME. Gemcitabine-mediated MDSC depletion and pharmacological STAT3 inhibition in tumor-associated antigen-presenting cells have demonstrated preclinical efficacy in bladder and renal cancer models specifically [25,29], while HDAC inhibitors targeting MDSC function are discussed more generally in a pan-cancer review of immunosuppressive cell populations, whose applicability to GU tumors specifically should be regarded as indirect evidence pending GU-focused preclinical confirmation [21]. MDSC-targeted strategies have also been investigated as a means of improving responses to immune checkpoint blockade by mitigating MDSC-associated immunosuppression [45]. Translating these insights into clinical combination strategies remains an active area of investigation.

Early-Phase Clinical Investigation

Therapeutic cancer vaccines are being developed as active immunization strategies to generate or amplify tumor-specific T-cell responses in the context of ICI resistance. As discussed in a GU-focused review of vaccine approaches, mRNA-based and DNA-based neoantigen vaccines, personalized to the mutational landscape of individual GU tumors, are under clinical evaluation in combination

Table 2. Tumor-type-specific summary of resistance mechanisms, predictive biomarkers, and therapeutic strategies in genitourinary cancers.

Tumor type	Dominant resistance mechanism(s)	Key predictive biomarkers	Most advanced therapeutic strategy
Urothelial carcinoma	Antigen-presentation defects (MHC-I downregulation [16]); compensatory checkpoint upregulation (LAG-3/TIM-3 [5,9])	PD-L1 IHC [10,33]; <i>APOBEC3B</i> signature [13]; high TMB (CheckMate 275) [36]	ICI + ADC (approved); ADCs — enfortumab vedotin, sacituzumab govitecan (approved); disitamab vedotin (HER2-positive, phase II) [41,42,43,44]
Renal cell carcinoma	TME-mediated immunosuppression — MDSC/Treg infiltration, CAF-mediated stromal exclusion, VEGF-driven vascular dysfunction [21,22,23,24,25,26,27]	Treg:CD8 ratio [23,26]; PD-L1 ⁺ MDSC density [24]	ICI + TKI — approved, guideline-embedded [42]
Prostate cancer (mCRPC)	Compound cold-tumor phenotype: low TMB/antigenicity [2,15] plus androgen-receptor-driven MDSC/TAM recruitment [28]	Limited validated biomarkers; smallest evidence base among GU subtypes (8/32 studies, 25.0%)	Radiotherapy as <i>in situ</i> vaccination + ICI (early-phase) [47]; therapeutic vaccines (early-phase) [46]

Abbreviations: TMB, tumor mutational burden; MHC-I, major histocompatibility complex class I; LAG-3, lymphocyte-activation gene 3; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; PD-L1, programmed death-ligand 1; TME, tumor microenvironment; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; CD8, cluster of differentiation 8 (cytotoxic T cell); CAF, cancer-associated fibroblast; VEGF, vascular endothelial growth factor; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mCRPC, metastatic castration-resistant prostate cancer.

with PD-1/PD-L1 blockade, with the objective of overcoming the insufficient immunogenicity that characterizes primary ICI resistance in antigenically cold tumors [46]. Radiotherapy combined with ICI is being explored as an *in situ* vaccination strategy, particularly in prostate cancer, where local irradiation induces immunogenic cell death, promotes tumor antigen release, and may convert an immunologically cold TME into an immune-permissive microenvironment amenable to checkpoint blockade, as discussed in a prostate-focused review [47].

Limited Clinical Evidence (Small Retrospective Series); Not Yet Validated in Phase III Trials

Sequential or rechallenge ICI administration following documented progression on a prior checkpoint inhibitor regimen has been evaluated in small series of patients with advanced urothelial carcinoma, revealing that a minority of patients may derive clinical benefit from such strategies, likely in the context of partially reversible resistance mechanisms [48]. The optimization of ICI sequencing within the broader therapeutic landscape — encompassing platinum-based chemotherapy, ADCs, targeted agents, and radiotherapy — represents an unresolved but clinically critical question for the management of ICI-resistant GU malignancies, as discussed in GU-focused reviews addressing this sequencing challenge [42,49,50].

To consolidate the tumor-type-specific patterns established throughout this synthesis, Table 2 (Ref. [2,5,9,10,13,15,16,21,22,23,24,25,26,27,28,33,36,41,42,43,44,46,47]), summarizes the dominant resistance mech-

anism, key predictive biomarkers, and most clinically advanced therapeutic strategy for each genitourinary cancer subtype.

Discussion

This integrative review consolidates evidence from 32 studies published between 2020 and 2026 to map the mechanistic landscape of ICI resistance in GU cancers, identify the most clinically actionable biomarkers, and delineate emerging therapeutic strategies. The synthesis reveals that ICI resistance is not a monolithic phenomenon but a continuum of biologically heterogeneous processes that differ in their principal drivers across tumor types, treatment lines, and individual patients.

The distinction between tumor cell-intrinsic mechanisms and TME-mediated immunosuppression carries fundamental implications for therapeutic strategy design. Intrinsic resistance driven by low TMB, antigen presentation defects, or activated immunosuppressive oncogenic signaling pathways—particularly Wnt/ β -catenin and JAK/STAT—is less likely to be overcome by ICI intensification alone and may require combination with agents that restore antigen immunogenicity, enhance MHC-I expression, or disrupt the relevant oncogenic pathway [4,19]. By contrast, TME-mediated resistance—driven by MDSC expansion, Treg accumulation, CAF-mediated stromal barrier formation, and immunosuppressive cytokine networks—is potentially amenable to pharmacological depletion or functional reprogramming of these cellular compartments [21,51].

A major finding of this review concerns the biomarker landscape. PD-L1 IHC retains clinical relevance as a regulatory decision-making tool but fails to capture the biological complexity of the tumor-immune interface across GU malignancies [10,11]. High TMB predicted superior pembrolizumab response in the pan-cancer KEYNOTE-158 analysis, with an ORR of 31.4% in TMB-high patients versus 9.5% in the low-TMB group [34], but histology-specific thresholds and assay standardization remain critical unresolved issues [12]. The evidence consistently supports a move toward composite, multi-dimensional biomarker panels that integrate PD-L1 expression, TMB, MHC-I pathway status, immune gene expression signatures, and neoantigen architecture [9,38]. The prospective clinical validation of such panels in GU-specific trial designs is urgently needed.

Regarding emerging therapeutic strategies, the ICI plus TKI paradigm has delivered the most robust clinical evidence and is now embedded in international treatment guidelines for advanced RCC and urothelial carcinoma. The mechanistic synergy between VEGF inhibition—which normalizes tumor vasculature and reduces MDSC accumulation—and PD-1/PD-L1 blockade is well-supported by the biological evidence synthesized here [27]. ADCs targeting nectin-4 and TROP-2 represent a paradigm shift for ICI-refractory urothelial carcinoma, and the activity of disitamab vedotin in HER2-positive disease—with an ORR of 50% in the combined phase II analysis—reinforces the relevance of molecular tumor subtyping for therapeutic selection [43]. Therapeutic vaccines and MDSC-directed strategies remain at earlier stages of clinical development but represent biologically grounded approaches for converting immunologically cold tumors into immune-responsive ones [25,46].

Several limitations inherent to integrative reviews must be acknowledged. Most directly, narrative and integrative reviews constituted the majority of included sources (62.5%, $n = 20/32$), and the substantial heterogeneity of study designs, cancer-type scope, and outcome reporting across the included evidence base restricts the strength of causal or quantitative inference that can be drawn; findings synthesized from secondary review sources should be regarded as hypothesis-generating rather than confirmatory pending GU-specific primary validation. The pan-cancer scope of several included mechanistic studies requires caution when extrapolating findings to specific GU tumor subtypes, as the immunological landscape of urothelial carcinoma, RCC, and prostate cancer differs substantially in terms of mutational burden, immune infiltration patterns, and oncogenic signaling dependencies. The rapid pace of regulatory approvals in this field also means that some findings presented may require updating as mature survival data from ongoing trials emerge. Finally, the substantial heterogeneity in study designs, populations, outcomes, and reported effect measures precluded meaningful quantitative synthesis.

Conclusions

ICI resistance in genitourinary cancers represents a biologically complex and clinically urgent challenge that demands a precision oncology approach. The dual targeting of tumor cell-intrinsic resistance drivers and the immunosuppressive TME through rational combination strategies offers the most promising path for expanding the reach of immunotherapy in these malignancies, though the strength of supporting evidence varies substantially by strategy and tumor type: ICI plus TKI combinations are already approved and guideline-embedded in RCC and advanced urothelial carcinoma, ICI plus ADC strategies are approved for selected agents but remain investigational for others (e.g., disitamab vedotin in HER2-positive disease), and ICI plus MDSC-directed interventions remain at the preclinical stage. Conclusions regarding the relative merit of these strategies should therefore be interpreted within each tumor type and clinical setting rather than as a uniform recommendation. The prospective validation of composite predictive biomarker platforms in GU-specific clinical trials must be prioritized to enable individualized therapeutic selection and to translate mechanistic insights into durable clinical benefit for the largest possible proportion of patients.

Availability of Data and Materials

Not applicable.

Author Contributions

AC is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

AI-assisted tools were used during the preparation of this manuscript in a strictly auxiliary capacity. Scite.ai (version: 1.40.0) was used for post-search bibliometric validation, including verification of citation context, retraction status, and metadata integrity of the included references. Paperpile (version: 1.5.1114) was used for reference management, including AI-assisted organizational functions. LanguageTool was used for targeted linguistic refinement in selected passages. After using AI-assisted tools, the author thoroughly reviewed, verified, and revised the manuscript to ensure the accuracy, originality, and integrity of its content.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.24976/Descov.Med.202638213.240>.

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