Review

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

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

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Abstract

Background: Immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 and 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. **Methods:** An integrative review was conducted following the Whittemore 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. Methodological quality was assessed using RoB 2, ROBINS-I, and AMSTAR-2 as appropriate. **Results:** 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 VEGF; and 3) acquired post-treatment resistance involving T-cell exhaustion and upregulation of alternative immune checkpoints. Among validated 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. **Conclusion:** ICI resistance in GU cancers is 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. Standardization of composite biomarker platforms is urgently needed to individualize ICI selection in clinical practice.

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

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1. 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 PD-L1, and cytotoxic T-lymphocyte antigen-4 (CTLA-4) have achieved regulatory approval across multiple indications, including locally advanced and metastatic urothelial carcinoma, advanced RCC, and a biomarker-selected subset of 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 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 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 [7,8]. 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 [9,10].

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 GU tumor types [11,12]. TMB has gained traction as a tumor-agnostic biomarker, yet substantial histology-specific variation limits its universal applicability [13]. Novel candidate biomarkers—including *APOBEC3B* mutational signatures, MHC-I expression, neoantigen clonality, and immune gene expression profiles—are under active investigation [14].

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.

2. Materials and Methods

2.1. Study Design and Methodological Framework

This study was conducted as an integrative review following the methodological framework proposed by Whittemore and Knafl [15]. 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.

2.2. 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 cov-

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ered 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. Four independent search sets were executed using combinations of the following terms and their MeSH equivalents: 1) "immune checkpoint inhibitor" AND "resistance" AND "genitourinary"; 2) "PD-L1" OR "PD-1" OR "CTLA-4" AND "biomarker" AND "renal cell carcinoma" OR "urothelial carcinoma" OR "prostate cancer"; 3) "tumor microenvironment" AND "immunosuppression" AND ("bladder cancer" OR "renal cell carcinoma"); and 4) "combination therapy" AND "checkpoint inhibitor" AND ("urothelial" OR "renal" OR "prostate"). The bibliometric integrity and contextual citation classification of all included references were verified using Scite.ai as a post-search validation tool.

2.3. 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 strategies to overcome ICI resistance; 4) were published in peer-reviewed journals between 2020 and 2026; and 5) were available in English. 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) consisted exclusively of case reports without cross-case synthesis; 3) were conference abstracts, editorials, or letters without sufficient methodological detail; or 4) were preprints without peer review.

2.4. 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.

2.5. Quality Assessment

Methodological quality was assessed using three validated instruments appropriate to the study design of each included source. No randomized or quasi-randomized trials were identified in the final corpus; the Risk of Bias 2 (RoB 2) tool [16] was therefore not applied. Observational studies were appraised using ROBINS-I [17], which evaluates seven domains: bias due to confounding; bias in selection of participants; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result. Systematic reviews and meta-analyses were evaluated using AMSTAR-2 [18]. The detailed domain-by-domain risk-of-bias assessment for each eligible primary study is presented in Appendix 1 (Tables A1 and A2). The overall integrity of included references was verified against the Scite.ai citation database to identify retractions, corrections, or published expressions of concern, none of which were detected in the final corpus.

3. Results

3.1. 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. The remaining 50 records were retrieved for full-text evaluation, of which 18 were subsequently excluded for the following reasons: non-GU focus without transferable mechanistic content (n = 9), exclusive case report 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 (Figure 1).

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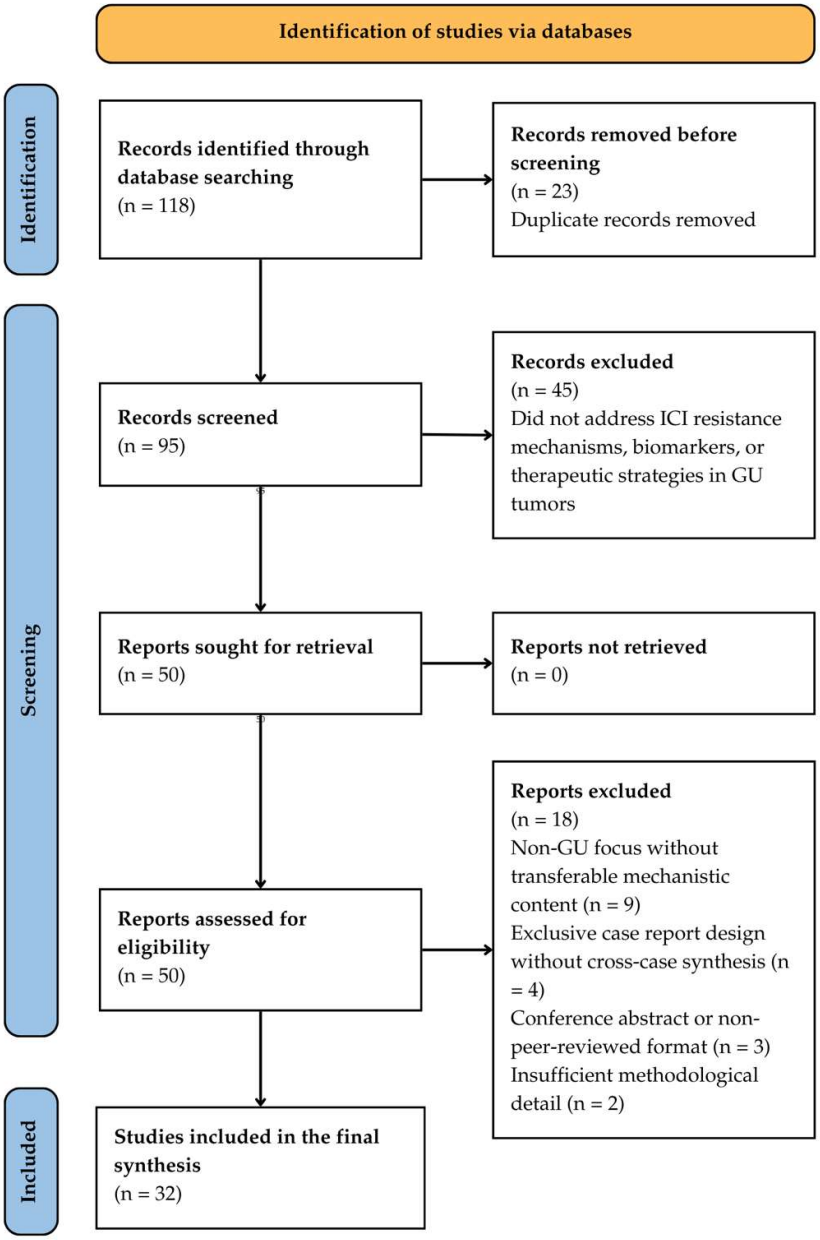

Figure 1. PRISMA flow diagram of the literature search and study selection process.

Among the 32 included studies, narrative and integrative reviews were the predominant design (n = 20; 62.5%), followed by original research articles (n = 10; 31.3%), case report/ex vivo study (n = 1; 3.1%), and a case series (3.1%). Urothelial carcinoma was the most frequently represented tumor type (62.5% of studies), followed by RCC (43.8%) and prostate cancer (25.0%); 31.3% of studies addressed multiple GU malignancies simultaneously. Most studies were conducted in North American or European settings (40.6%), with a substantial proportion employing multinational or pan-cancer populations (37.5%), followed by Asia-Pacific settings (15.6%) and mixed or unspecified populations (6.3%). The primary ICI agents evaluated were pembrolizumab (62.5%) and nivolumab (53.1%), either as monotherapy or in combination regimens, followed by atezolizumab/avelumab (37.5%) and ipilimumab (28.1%). The risk-of-bias assessment indicated low risk in 34.4% of studies, moderate risk in 46.9%, and high risk in 18.8%, based on ROBINS-I for the 12 non-randomized observational studies and AMSTAR-2 for the 20 narrative and systematic reviews. The general characteristics of the included studies are summarized in Table 1.

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Table 1. General characteristics of the 32 included studies.

Characteristic	n (%)	Detail / Range
Number of included studies	32	—
Geographic distribution		
Multinational / pan-cancer	12 (37.5%)	—
North America / Europe	13 (40.6%)	—
Asia-Pacific	5 (15.6%)	—
Mixed / not specified	2 (6.3%)	—
Methodological design		
Narrative / integrative review	20 (62.5%)	—
Original research article	10 (31.3%)	—
Case report / ex vivo 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%)	
Primary cancer types *(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
ICI agents evaluated *(non-exclusive)*		
Nivolumab (anti-PD-1)	17 (53.1%)	—
Pembrolizumab (anti-PD-1)	20 (62.5%)	—
Atezolizumab / Avelumab (anti-PD-L1)	12 (37.5%)	—
Ipilimumab (anti-CTLA-4)	9 (28.1%)	—
Risk-of-bias assessment		
Low risk	11 (34.3%)	RoB 2 / AMSTAR-2 applied
Moderate risk	15 (46.9%)	ROBINS-I applied
High risk	6 (18.8%)	Predominantly non-randomized designs

3.2. Tumor Cell-Intrinsic Mechanisms of Resistance

Several tumor cell-intrinsic mechanisms have been identified as major determinants of primary ICI resistance across GU malignancies. Among the most well-characterized is the absence of immunogenic antigenicity resulting from low TMB. Tumors with a paucity of somatic mutations generate insufficient neoantigens to trigger effective T-cell recognition, thereby precluding productive anti-tumor immune responses [4,13]. Prostate cancer epitomizes this paradigm, typically harboring a low mutational load that contributes to its immunologically cold phenotype and the historically limited efficacy of ICI in unselected populations [2,19].

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Downregulation of antigen presentation machinery, particularly MHC class I expression, represents a second critical intrinsic resistance mechanism. 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 [7,10]. In urothelial carcinoma, 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 [20].

Activation of oncogenic signaling pathways provides an additional layer of intrinsic resistance. 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 [8,21]. *JAK1*/*JAK2* mutations, identified in patients with acquired resistance to PD-1 blockade, ablate IFN-γ signaling and disrupt downstream antigen presentation upregulation, undermining the immunostimulatory effect of ICI [4,7].

Epigenetic reprogramming constitutes a particularly dynamic and therapeutically tractable resistance mechanism. 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 [22,23]. In bladder and renal cancers, lncRNAs have been shown to regulate drug resistance pathways across multiple therapeutic contexts [23], and emerging evidence 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 [24].

3.3. 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. MDSCs—encompassing granulocytic (G-MDSCs) and monocytic (M-MDSCs) subpopulations—are prominently expanded in the TME of urothelial carcinoma and RCC. 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 [25–27]. 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 [28,29]. 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 [30].

Tregs represent a second major immunosuppressive cellular component of the GU tumor immune microenvironment, suppressing 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 [25,26]. In clear-cell RCC (ccRCC), the ratio of Tregs to cytotoxic T cells represents a prognostic and potentially predictive variable for ICI response [28,31].

CAFs contribute to physical and biochemical barriers to immune infiltration. In ccRCC, CAF subpopulations characterized by diverse functional states—including myofibroblastic, inflammatory, and immunosuppressive phenotypes—create a stromal barrier that impedes effector T-cell trafficking into tumor parenchyma while actively secreting VEGF and TGF-β [31,32]. 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

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inflammatory response that is subsequently counteracted by adaptive immunosuppressive remodeling of the TME [33]. *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 [34].

3.4. 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 LAG-3, TIM-3, and TIGIT—that diminishes cytolytic capacity and proliferative potential, rendering cells unresponsive to further PD-1 blockade [9,35].

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; 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 [5,10]. Tumor immunological heterogeneity—encompassing both spatial and temporal variability in antigen expression and immune infiltration—further complicates the maintenance of durable responses [13].

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 [36]. 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 [37].

3.5. Predictive Biomarkers

The validation of reliable predictive biomarkers for ICI response in GU malignancies has been a principal focus of translational oncology research. PD-L1 expression, measured by IHC, remains the most extensively evaluated biomarker and is incorporated into the regulatory approval label for several ICI indications. However, 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 [11,38]. 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 [14].

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 [39]. 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 [13,40]. 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 [41].

Emerging 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 [14]; neoantigen clonality, which captures the proportion of mutations present in all tumor clones and provides

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a more refined measure of immunogenic antigenicity than TMB alone [36]; MHC-I pathway integrity, including HLA-I expression and B2M status, which predicts the capacity for neoantigen presentation and T-cell recognition [20]; POLQ (DNA polymerase theta), identified as a marker of a better-responding immunotherapy subset in muscle-invasive bladder cancer with high PD-L1 expression [42]; and composite immune gene expression signatures including the 18-gene tumor inflammation signature and interferon-γ gene expression profiles [43]. Machine learning approaches applied to transcriptomic data across urothelial carcinoma and RCC patients 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 [43]. The role of the microbiome as a systemic immune modulator is also emerging as a relevant biological determinant of ICI response in bladder cancer [44].

3.6. Emerging Therapeutic Strategies to Overcome Resistance

The co-administration of ICI with VEGF-targeted 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 [45]. 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 [46,47].

ADCs have emerged as a transformative modality for patients with ICI-refractory GU tumors. Enfortumab vedotin, targeting nectin-4 on urothelial carcinoma cells, and sacituzumab govitecan, targeting TROP-2, have 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 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 [48]. Nectin-4 and PD-L1 co-expression patterns in bladder cancer further inform the rational selection of ADC plus ICI combination strategies [46,49].

MDSC-targeted therapeutic strategies constitute a mechanistically grounded approach to reprogramming the immunosuppressive TME. Gemcitabine-mediated MDSC depletion, HDAC inhibitors targeting MDSC function, and pharmacological STAT3 inhibition in tumor-associated antigen-presenting cells have each demonstrated preclinical efficacy in bladder and renal cancer models [30,34,50]. Translating these insights into clinical combination strategies remains an active area of 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. mRNA-based and DNA-based neoantigen vaccines, personalized to the mutational landscape of individual GU tumors, are under clinical evaluation in combination with PD-1/PD-L1 blockade, with the objective of overcoming the insufficient immunogenicity that characterizes primary ICI resistance in antigenically cold tumors [51]. 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 [52].

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 [53]. 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 [47,54,55].

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4. 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 [4,22]. 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 [25,32].

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 [11,12]. 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 [39], but histology-specific thresholds and assay standardization remain critical unresolved issues [13]. 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 [10,43]. 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 [46]. 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 [48]. 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 [30,51].

Regarding the sample of included studies, the predominance of North American and European populations (40.6%) combined with the multinational representation (37.5%) provides a geographically diverse evidence base, though the limited representation of Asia-Pacific settings (15.6%) warrants caution when generalizing findings to populations with potentially distinct germline immune profiles, microbiome compositions, and treatment access patterns. Similarly, the high proportion of narrative and integrative review designs (56.3%) means that many mechanistic and biomarker insights derive from synthesized rather than primary evidence, with the associated risk of amplifying positive-reporting biases from the primary literature.

Several limitations inherent to integrative reviews must be acknowledged. 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 absence of patient-level data prevents quantitative meta-analytic synthesis, limiting conclusions to qualitative integration of effect estimates.

In conclusion, ICI resistance in genitourinary cancers represents a biologically complex and clinically urgent challenge that demands a precision oncology approach. The dual targeting of tumor

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cell-intrinsic resistance drivers and the immunosuppressive TME through rational combination strategies—particularly ICI plus TKI, ICI plus ADC, and ICI plus MDSC-directed interventions—constitutes the most evidence-supported direction for expanding the reach of immunotherapy in these malignancies. 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.

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Data Availability Statement: Not applicable.
Conflicts of Interest: The author declares no conflict of interest.

Appendix 1

Table A1. ROBINS-I Assessment (Non-randomized and observational studies, n = 12).

Study	Study design	Cancer type	D1	D2	D3	D4	D5	D6	D7	Overall risk
Alcantara et al. [34]	Original research (preclinical + phase I)	RCC + Bladder	**L**	M	**L**	**L**	**L**	**L**	**L**	**L**
Altomare et al. [6]	Retrospective case series	mCRPC	M	M	**L**	M	M	M	**L**	M
Banchereau et al. [43]	Retrospective cohort	UC / RCC / NSCLC	M	**L**	**L**	**L**	M	**L**	**L**	M
Bazargan et al. [30]	Preclinical experimental	Bladder	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Boll et al. [36]	Retrospective cohort	UC (advanced)	M	M	**L**	**L**	M	**L**	**L**	M
Cristescu et al. [39]	Retrospective pan-tumor cohort	Multiple solid tumors	M	**L**	**L**	**L**	M	**L**	**L**	M
Huang RSP et al. [38]	Retrospective cohort	UC	M	**L**	**L**	**L**	M	**L**	**L**	M
Jindal et al. [53]	Case series	UC (advanced)	**H**	**H**	M	M	**H**	M	**L**	**H**
Kim H et al. [40]	Retrospective cohort	GU + GI solid tumors	M	M	**L**	**L**	M	M	**L**	M
Kusmartsev et al. [29]	Case report / ex vivo	RCC	**H**	**H**	**L**	M	**H**	M	**L**	**H**
Liu G et al. [42]	Retrospective cohort	UC (MIBC)	M	M	**L**	**L**	M	**L**	**L**	M
Martini et al. [49]	Retrospective cohort	UC (bladder)	M	**L**	**L**	**L**	M	**L**	**L**	M

Note: Assessment performed using ROBINS-I for non-randomized and observational studies and AMSTAR-2 for narrative and systematic reviews. No randomized controlled trials were included in the final corpus; the RoB 2 tool was therefore not applied. Risk-of-bias judgments reflect available information from each publication. ROBINS-I domains: D1, Bias due to confounding; D2, Bias in selection of participants into the study; D3, Bias in classification of interventions; D4, Bias due to deviations from intended interventions; D5, Bias due to missing

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data; D6, Bias in measurement of outcomes; D7, Bias in selection of the reported result. Abbreviations: L = Low risk / High confidence; M = Moderate risk; H = High risk / Low confidence.

Table A2. AMSTAR-2 Assessment (Narrative and systematic reviews, n = 20).

Study	Study design	Cancer type	I1	I2	I3	I4	I5	I6	I7	I8	Overall confidence
Barth et al. [23]	Narrative review	GU (RCC, Bladder, Prostate)	NR	M	M	M	M	**L**	N/A	**L**	M
Berland et al. [9]	Narrative review	Multiple solid tumors	NR	M	M	**L**	M	M	N/A	**L**	M
Coschi & Juergens [35]	Narrative review	Multiple solid tumors (incl. GU)	NR	M	M	**L**	M	M	N/A	**L**	M
Di Martino et al. [24]	Narrative review	Multiple cancers (incl. GU)	NR	M	M	**L**	M	M	N/A	**L**	M
Fujiwara et al. [21]	Narrative review	Multiple solid tumors	NR	**H**	**H**	**H**	**H**	**H**	N/A	**L**	**H**
Germana et al. [11]	Narrative review	UC (bladder, advanced)	NR	M	M	M	M	M	N/A	**L**	M
Haist et al., 2021 [26]	Narrative review	Multiple solid tumors (incl. GU)	NR	M	M	**L**	M	M	N/A	**L**	M
Hui et al., 2023 [55]	Narrative review	UC (advanced/metastatic)	NR	**L**	**L**	**L**	M	**L**	N/A	**L**	**L**
Jackson-Spence et al. [47]	Narrative review	GU (RCC, UC, Prostate)	NR	**L**	**L**	**L**	M	**L**	N/A	**L**	**L**
Khaki et al. [54]	Perspective / narrative review	UC (advanced)	NR	**H**	**H**	**H**	**H**	**H**	N/A	**L**	**H**
Koustas et al. [4]	Narrative review	Multiple solid tumors	NR	M	M	M	M	M	N/A	**L**	M
Labadie et al. [1]	Narrative review	GU (UC, RCC, Prostate, Testicular)	NR	**L**	**L**	**L**	M	**L**	N/A	**L**	**L**
Lanka et al. [2]	Narrative review	mCRPC	NR	M	M	**L**	M	M	N/A	**L**	M
Li T et al. [52]	Narrative review	Prostate	NR	M	M	**L**	M	M	N/A	**L**	M
Li X et al. [50]	Narrative review	Multiple cancers (incl. GU)	NR	M	M	**L**	M	M	N/A	**L**	M
Maiorano et al. [45]	Narrative / systematic review	UC (advanced/metastatic)	**L**	**L**	**L**	**L**	M	**L**	N/A	**L**	**L**
Marei et al. [5]	Narrative review	Multiple solid tumors (incl. GU)	NR	M	M	**L**	M	M	N/A	**L**	M
Meyers & Banerji [12]	Narrative review	Multiple cancers (incl. GU)	NR	**L**	**L**	**L**	M	**L**	N/A	**L**	**L**

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Study	Study design	Cancer type	I1	I2	I3	I4	I5	I6	I7	I8	Overall confidence
Monjarás-Ávila et al. [31]	Narrative review	ccRCC	NR	M	M	**L**	M	M	N/A	**L**	M
Perrier et al. [22]	Narrative review	Multiple solid tumors	NR	M	M	**L**	M	M	N/A	**L**	M

Note: AMSTAR-2 items: I1, Protocol registration; I2, Comprehensiveness of search strategy; I3, Duplicate study selection; I4, Full-text screening with justification of exclusions; I5, Data extraction in duplicate; I6, Assessment of risk of bias in included primary studies; I7, Appropriateness of meta-analytic methods; I8, Consideration of funding bias in included studies. I7 was not applicable (N/A) to all narrative reviews, as no quantitative synthesis was performed. Abbreviations: L = Low risk / High confidence; M = Moderate risk; H = High risk / Low confidence; NR = Not reported N/A = Not applicable.

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